

Cardiovascular system

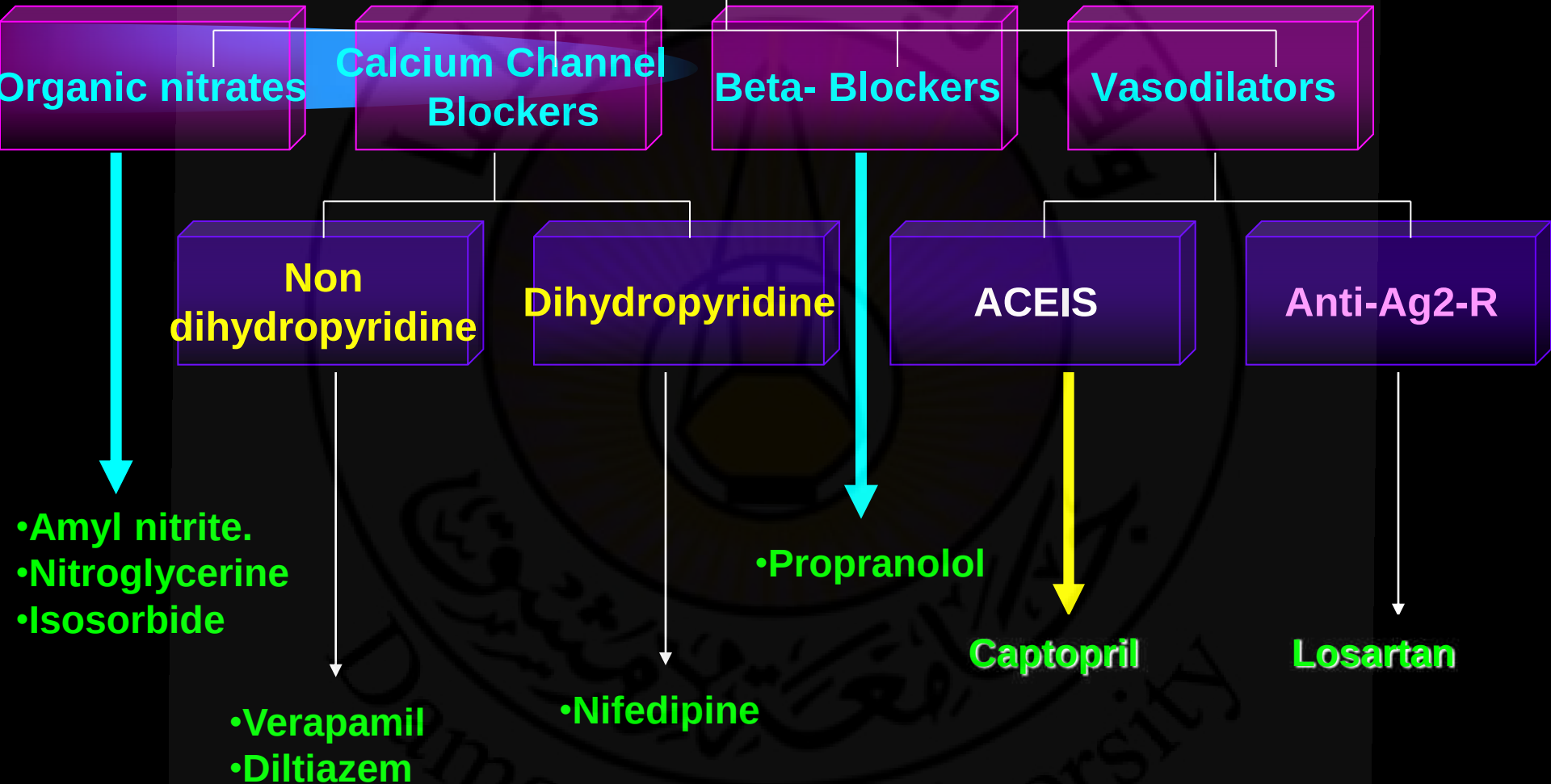


Angina



*Pressure in the chest
following physical exercise
may be a sign of Angina.*

Antianginal drugs by class



These medications work via vasodilation to increase blood flow and / or decrease heart rate and, therefore, decrease cardiac oxygen demand.

Pharmacokinetics

Amyl nitrite

-  **A:** Inhalation of volatile substance.
-  **M:** Rapidly metabolized.
-  **E:** One third excreted unchanged in urine.

Pharmacokinetics

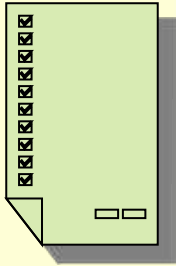
Nitroglycerine

-  **A:** Sublingual, PO, IV, ointment, or patches.
-  **M:** Hepatic metabolism to active metabolites.

Pharmacokinetics

Iosorbide dinitrate

- ❏ **A:** Sublingual, PO, IV, ointment, or patches.
- ❏ **M:** Hepatic metabolism to active metabolites.
- ❏ **E:** Metabolites excreted in urine .



Mechanism of action



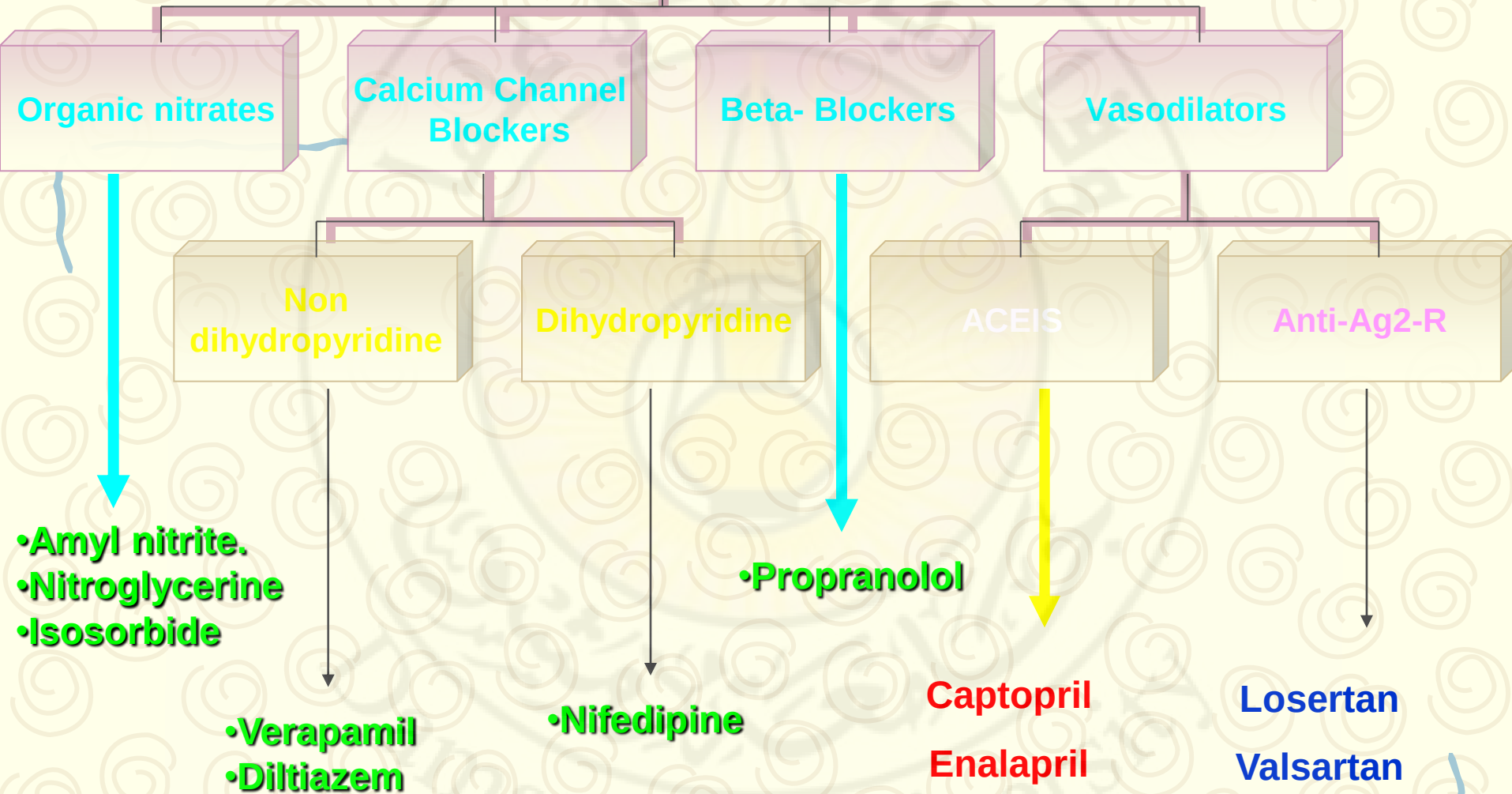
- **Converted to nitric oxide intracellularly, which activates guanylate cyclase, leading to the following cascade of events:**
 - ✓ **Leading to an increase in cGMP.**
 - ✓ **Causing dephosphorylation of myosin light chain.**
 - ✓ **Leading to relaxation of vascular smooth muscle resulting in vasodilation.**
- **Venous dilation decreases preload.**
- **Vasodilation increase blood flow to myocardium.**

Side effects



- ⇒ **Headache.**
- ⇒ **Repeated administration leads to a loss of effectiveness. (tolerance)**
- ⇒ **Large degree of cross tolerance between organic nitrates.**
- ⇒ **Systemic compensation (salt and water retention) may also be involved in loss of effectiveness.**

Antianginal drugs by class



These medications work via vasodilation to increase blood flow and / or decrease heart rate and, therefore, decrease cardiac oxygen demand.

Pharmacokinetics

Verapamil

-  **A:** PO and IV.
-  **M:** Extensive first - pass hepatic metabolism; metabolized by P450 enzymes to active metabolite.
-  **E:** In urine and feces.

Diltiazem

-  **A:** PO and IV.
-  **M:** Extensive first - pass hepatic metabolism; metabolized by P450 enzymes to less active metabolites.
-  **E:** In urine and feces.



Mechanism of action

- ❖ ***Reduce Ca^{+2} influx.***
- ❖ ***Resulting reduction of IC Ca^{+2} leads to smooth muscle relaxation.***
- ❖ ***Result in decreased myocardial contractile force and decreased arterial tone and systemic vascular resistance.***

Voltage Sensitive Calcium Channels

	L-type (Long lasting current)	T-type (Transient current)	N-type (Neuronal)
1. Conductance	25 pS	8 pS	12-20 pS
2. Activation threshold	High	Low	High
3. Inactivation rate	Slow	Fast	Medium
4. Location and Function	• Excitation-contraction coupling in cardiac and smooth muscle • SA, A-V node—conductivity • Endocrine cells—hormone release • Neurones—transmitter release	• SA node—pace-maker activity • 'T' current and repetitive spikes in thalamic and other neurones • Endocrine cells—hormone release • Certain arteries—constriction	• Only on neurones in CNS, sympathetic and myenteric plexuses—transmitter release
5. Blocker	Nifedipine, diltiazem, verapamil	Mibefradil, flunarizine, ethosuximide	ω -Conotoxin



Verapamil

- **Stable, unstable, and variant angina.**
- **Supraventricular arrhythmias.**
- **Ventricular rate control in atrial flutter and fibrillation.**
- **Hypertension.**



Diltiazem

- **Stable and variant angina.**
- **Supraventricular arrhythmias.**
- **Ventricular rate control in atrial flutter and fibrillation.**
- **Hypertension.**

Side effects



- ❖ **Bradycardia.**
- ❖ **Constipation.**
- ❖ **Decreased cardiac contractility.**
- ❖ **Hypotension.**
- ❖ **Increases digoxin levels.**

Side effects



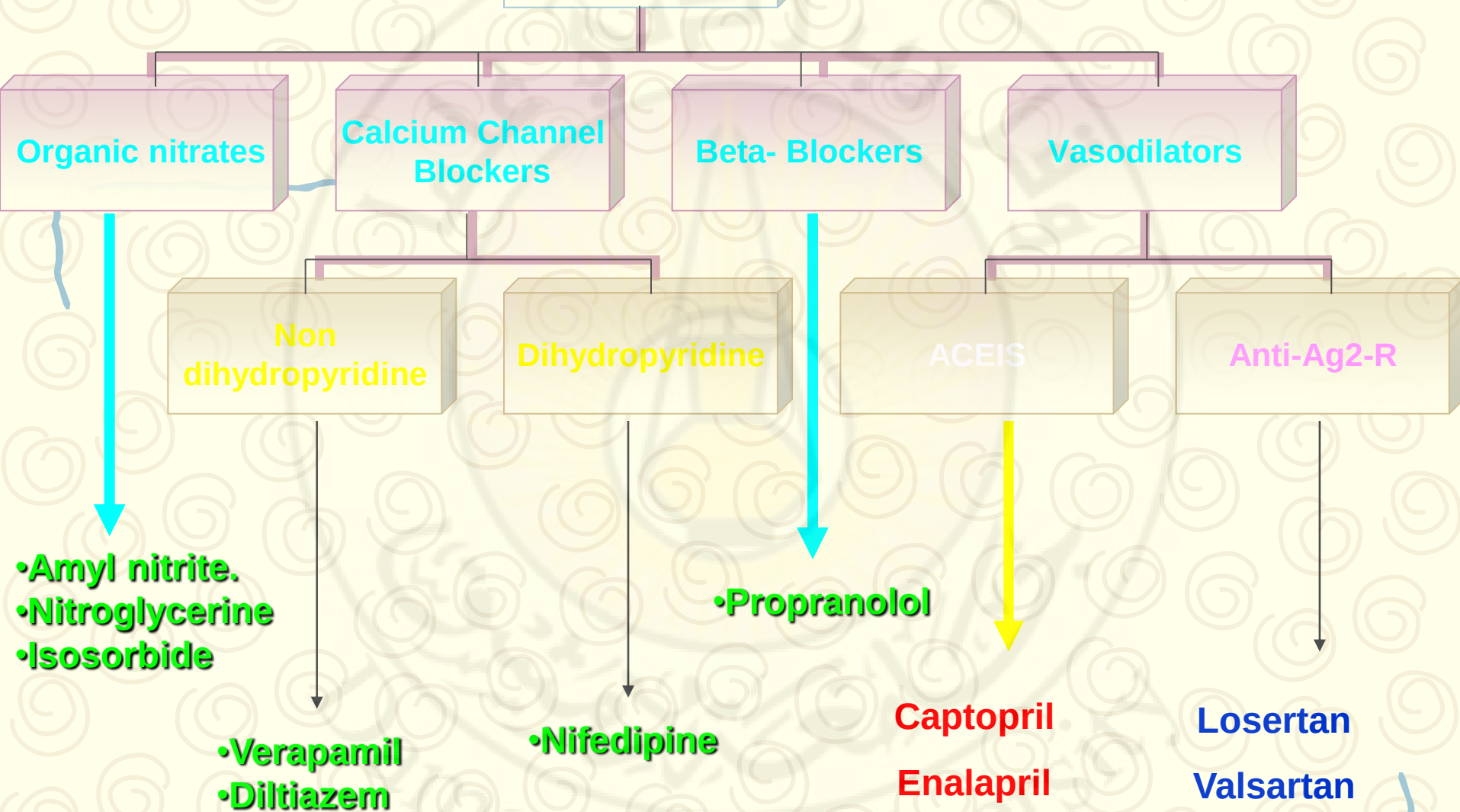
- ❖ **Bradycardia.**
- ❖ **Hypotension.**
- ❖ **Decreased cardiac contractility.**

Side effects



- ❖ **Flushing.**
- ❖ **Headache.**
- ❖ **Hypotension (rapid decrease in BP can exacerbate ischemia).**
- ❖ **Peripheral edema.**
- ❖ **Reflex tachycardia.**

Antianginal drugs by class



These medications work via vasodilation to increase blood flow and / or decrease heart rate and, therefore, decrease cardiac oxygen demand.



❖ Propranolol

❏ **A:** PO and IV.

❏ **M:** Extensive first- pass hepatic metabolism.

❏ **E:** Parent drug and metabolites excreted in urine and feces.

Mechanism of action

Propranolol

- Decreases heart rate and contractility to reduce oxygen demand of the heart.
- Increases time in diastole.
- Increases coronary blood flow.
- Increase exercise tolerance and duration.
- Decreases frequency and severity of angina attacks.

Propranolol

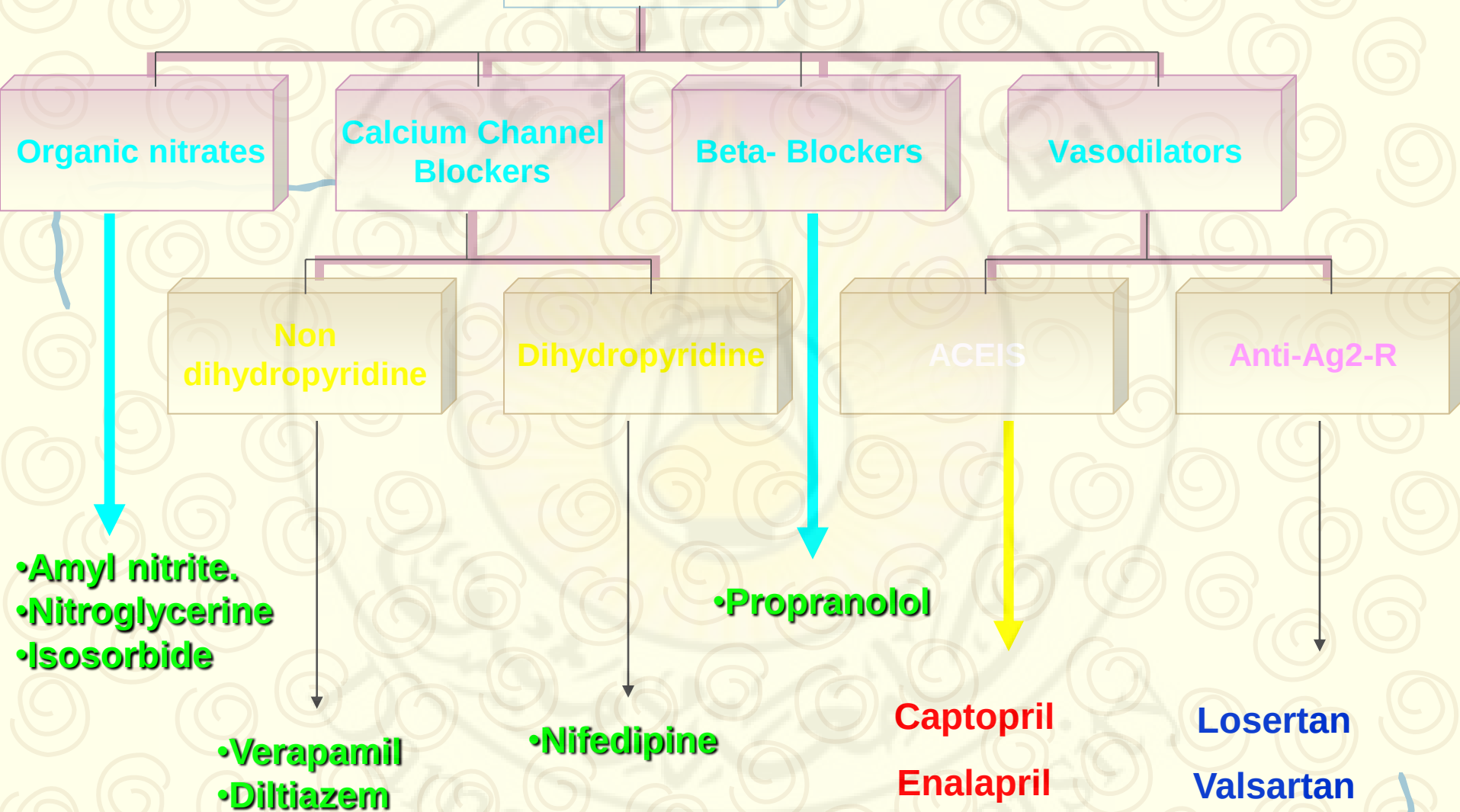
- **Stable and unstable angina.**
- **Often used in combination with nitrates or calcium channel blockers.**

Drawbacks and Side effects

Propranolol

- *Contraindicated in patients with asthma, diabetes, PVD, or COPD.*
- *Combining carefully with verapamil and diltiazem because additive negative inotropic effects lead to bradyarrhythmias.*

Antianginal drugs by class

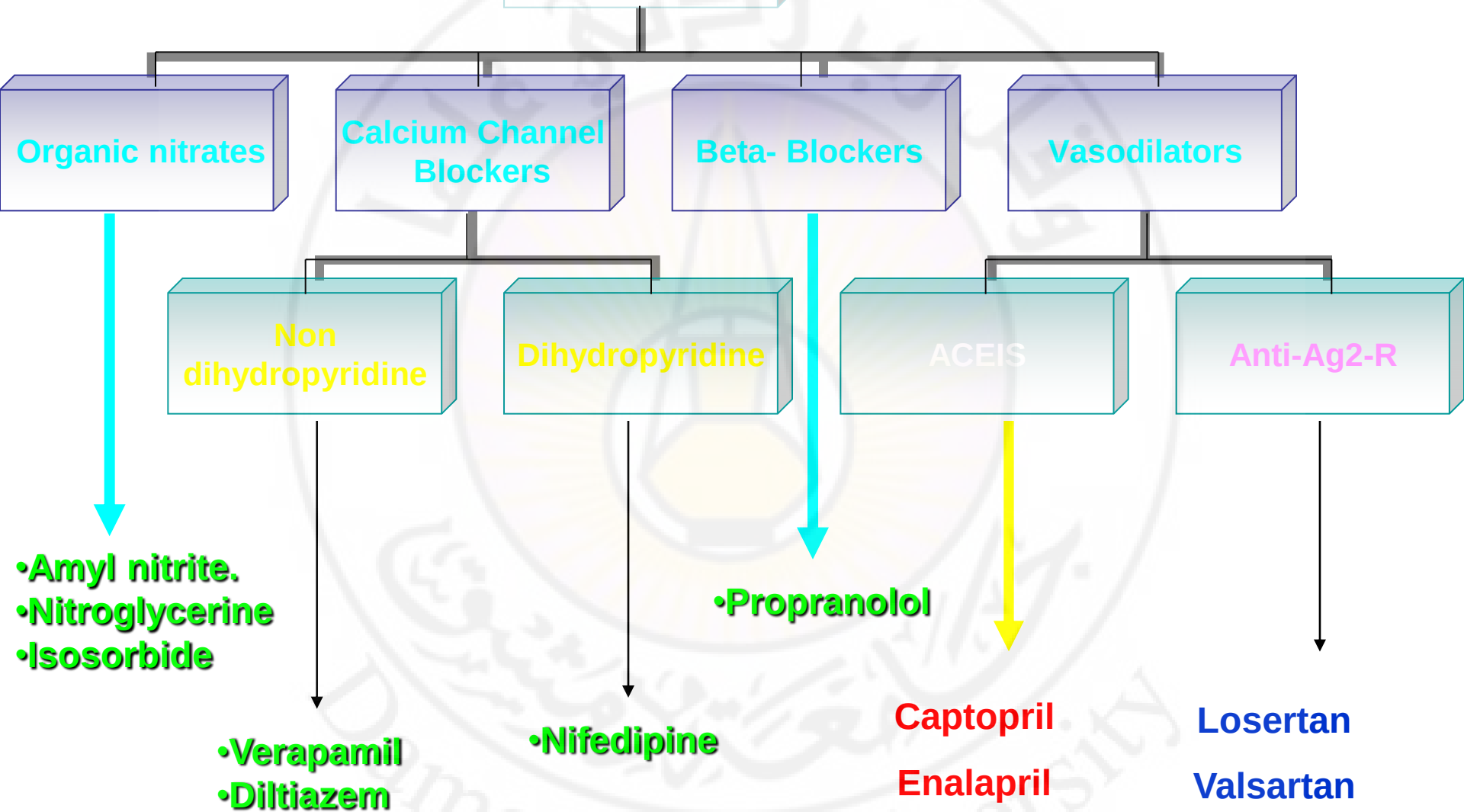


These medications work via vasodilation to increase blood flow and / or decrease heart rate and, therefore, decrease cardiac oxygen demand.

Side effects

- ❖ *Bradykinin increase leading to cough and skin rash.*
- ❖ *Teratogenesis.*
- ❖ *Hypokalemia.*
- ❖ *Neutropenia.*
- ❖ *Hypotension.*
- ❖ *Acute renal failure.*

Antianginal drugs by class



These medications work via vasodilation to increase blood flow and / or decrease heart rate and, therefore, decrease cardiac oxygen demand.

Pharmacokinetics



 **A:** PO.

 **M:** Hepatic metabolism by P450 system.

 **E:** Parent drug and metabolite excreted in urine and feces.

Losartan & Valsartan

- Angiotensin I receptor blockade prevents the vasoconstriction caused by Angiotensin I.

Clinical Uses



**Losartan
&
Valsartan**

❖ **Hypertension.**

❖ **CHF**

Side effects

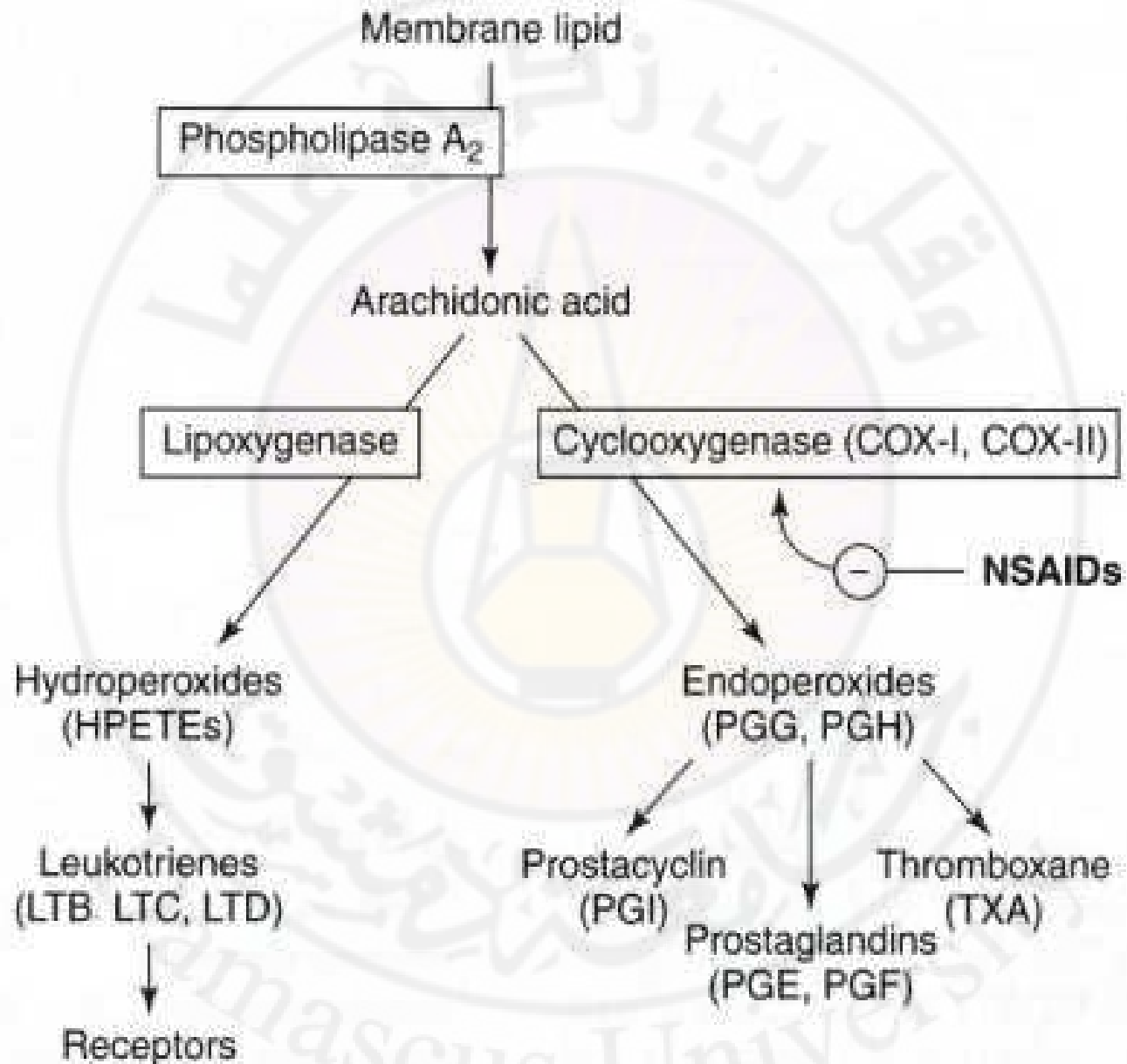


Losartan & Valsartan

- ❖ Smaller incidence of side effects than ACE inhibitor.
- ❖ No bradykinin increase (no cough or rash)

Aspirin

Low dose (75–300 mg) aspirin reduces the risk of adverse events such as myocardial infarction and should be prescribed for all patients with coronary artery disease unless it causes troublesome dyspepsia or other side-effects.



- There is now evidence that high doses of vitamin Vit E (α -tocopheryl acetat) can usefully reduce the risk of myocardial infraction in patients with severe coronary disease.
- It is important to remember the objective of preventing complications, particularly, myocardial infraction and sudden death. This requires vigorous treatment of all risk factors hypertension, hyperlipideamia, diabetes, and of course no smoking.

Risk Factors

- *Smoking*
- *High blood pressure*
- *Raised cholesterol levels*
- *Increased age*
- *Diabetes*
- *Hereditary heart disease*
- *Obesity*
- *Lack of exercise*
- *Old age*

What to do during an *Angina* attack

At the first sign of chest pain:

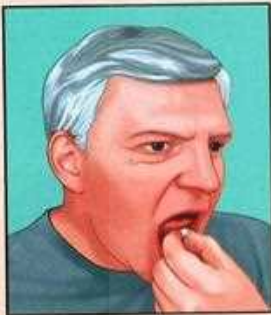


1. Sit down and rest immediately. Wait for a few minutes.

2. If symptoms are not gone in 2-3 minutes, place your **FIRST** *nitroglycerin* tablet under your tongue (or between your gum and inside cheek), or use your spray.

- Do not chew or swallow the tablet.
- Do not drink, eat, or smoke while the nitroglycerin is in your mouth.

You may experience a slight stinging or burning sensation. This is normal and means the *nitroglycerin* is working.

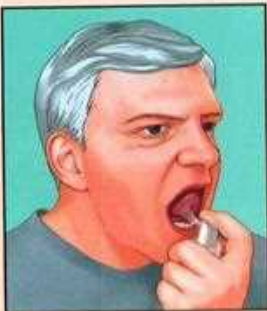


Place the tablet under your tongue and allow it to dissolve.

3. If the symptoms still persist after a further 3-5 minutes, use a **SECOND** tablet (or spray).

4. Wait 3-5 minutes and if symptoms still persist, use a **THIRD** tablet (or spray).

5. If your *Angina* is still present after the **THIRD** tablet (or spray), and at least 15 minutes after you first started to feel discomfort, call your healthcare provider, or ask someone to take you to the nearest hospital emergency room.



Spray directly under your tongue.
DO NOT INHALE

5. Self Help

It is important to always keep warm.

A well-balanced diet, involving a reduction of dietary fats, may help to maintain recommended body weight.



A normal lifestyle should be maintained, with regular physical exercise, approved by your healthcare provider, which does not produce any pain or discomfort.



STOP SMOKING



If you are able to climb up and down two flights of stairs (26 steps in total) without experiencing any discomfort, intimate activities with your partner can be resumed.



Regular check-ups will also enable your healthcare provider to monitor your condition.

RANOLAZINE

Act by reducing a late sodium current(I_{Na}) that Facilitates calcium entry via the sodium-calcium

Exchanger $\rightarrow \downarrow I_{cca++} \rightarrow \downarrow c_{op} \rightarrow \downarrow O^2$
demand

TRIMETAZIDINE (p FOX inhibitor)

Partially inhibits the fatty acid oxidation pathway In myocardium $\rightarrow \downarrow \text{O}_2$ requirement.

ALLOPURINOL

- Inhibits xanthine oxidase , an enzyme that contributes to oxidative stress and endothelial dysfunction.

IVABRADINE

Acts by inhibiting Na^+ channel in
the SA-node $\rightarrow$ Bradycardic drug
 $\rightarrow \downarrow \text{O}_2$ demand $\rightarrow \downarrow$ attack = (ccb, β b)
without SE on Bronchial or GIT.

FASUDIL

Is an inhibitor of smooth muscle Rho-kinase (that inhibits vascular relaxation)
→ ↓ coronary vasospasm.

Risk Factors

- *Smoking*
- *High blood pressure*
- *Raised cholesterol levels*
- *Increased age*
- *Diabetes*
- *Hereditary heart disease*
- *Obesity*
- *Lack of exercise*
- *Old age*

Table 37.1: Organic nitrates available for angina pectoris

<i>Drug</i>	<i>Preparations</i>	<i>Dose & Route</i>	<i>Duration of action</i>
1. GTN (Nitroglycerine)	ANGISED 0.5 mg tab	0.5 mg sublingual	10-30 min
	NITROLINGUAL, GTN spray	0.4-0.8 mg s.l. spray	10-30 min
	0.4 mg per spray		
	ANGISPAN-TR 2.5, 6.5 mg SR cap.	5-15 mg oral	4-8 hr
	NITROCONTIN 2.6, 6.4 mg tabs.		
2. Isosorbide dinitrate	NITRODERM-TTS 5 or 10 mg patch	One patch for 14-16 hr per day	Till applied, max 24 hr.
	MYOVIN, NITROJECT 5 mg/ml inj	5-10 µg/min i.v.	till infused
	SORBITRATE 5, 10 mg tab,	5-10 mg sublingual	20-40 min
	ISORDIL 5 mg sublingual & 10 mg oral tab.	10-20 mg oral	2-3 hr
	DITRATE 5,10 mg tab; 20,40 mg SR tab	20-40 mg oral	6-10 hr
3. Isosorbide-5-mononitrate	MONOTRATE 10, 20, 40 mg tab, 50 mg SR tab,	20-40 mg oral	6-10 hr
	5-MONO, MONOSORBITRATE 10, 20, 40 mg tab.		
4. Erythrityl-tetranitrate	CARDILATE 5, 15 mg tab	15-60 mg oral	4-6 hr
5. Pentaerythritoltetranitrate	PERITRATE 10 mg tab	10-40 mg oral	3-5 hr
	PERITRATE-SA 80 mg SR tab	80 mg oral	8-12 hr

Table 37.2: Comparative properties of representative Calcium Channel Blockers

	<i>Verapamil</i>	<i>Nifedipine</i>	<i>Diltiazem</i>
1. Channel blocking potency	++	+++	+
2. Frequency dependence of channel blockade	++	-	+
3. Channel recovery rate	Much delayed	No effect	Delayed
4. Cardiac effects (<i>In vivo</i> at usual clinical doses)			
Heart rate	↓	↑	↓, -
A-V Conduction Velocity	↓↓	-	↓
Contractility	-, ↓	↑	↓, ↑
Output	-, ↓	↑	-, ↑
5. Vascular smooth muscle relaxation	++	+++	+
6. Clinical use in	Angina Arrhythmia (Hypertension)	Angina Hypertension	Angina Hypertension (Arrhythmia)

What to do during an *Angina* attack

At the first sign of chest pain:

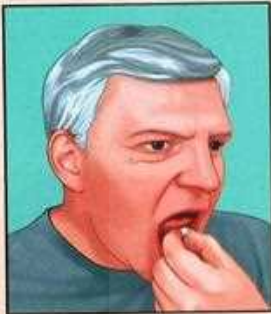


1. Sit down and rest immediately. Wait for a few minutes.

2. If symptoms are not gone in 2-3 minutes, place your **FIRST** *nitroglycerin* tablet under your tongue (or between your gum and inside cheek), or use your spray.

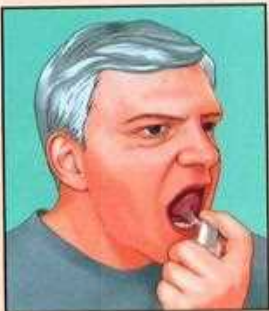
- Do not chew or swallow the tablet.
- Do not drink, eat, or smoke while the nitroglycerin is in your mouth.

You may experience a slight stinging or burning sensation. This is normal and means the *nitroglycerin* is working.



Place the tablet under your tongue and allow it to dissolve.

3. If the symptoms still persist after a further 3-5 minutes, use a **SECOND** tablet (or spray).



Spray directly under your tongue.
DO NOT INHALE

4. Wait 3-5 minutes and if symptoms still persist, use a **THIRD** tablet (or spray).

5. If your *Angina* is still present after the **THIRD** tablet (or spray), and at least 15 minutes after you first started to feel discomfort, call your healthcare provider, or ask someone to take you to the nearest hospital emergency room.



Coronary Heart Disease (CHD)

Antianginal Drugs



Antihyperlipidemic Drugs

Drugs affecting Coagulation

شكراً على الإصغاء

Damascus University

Seventh Lecture

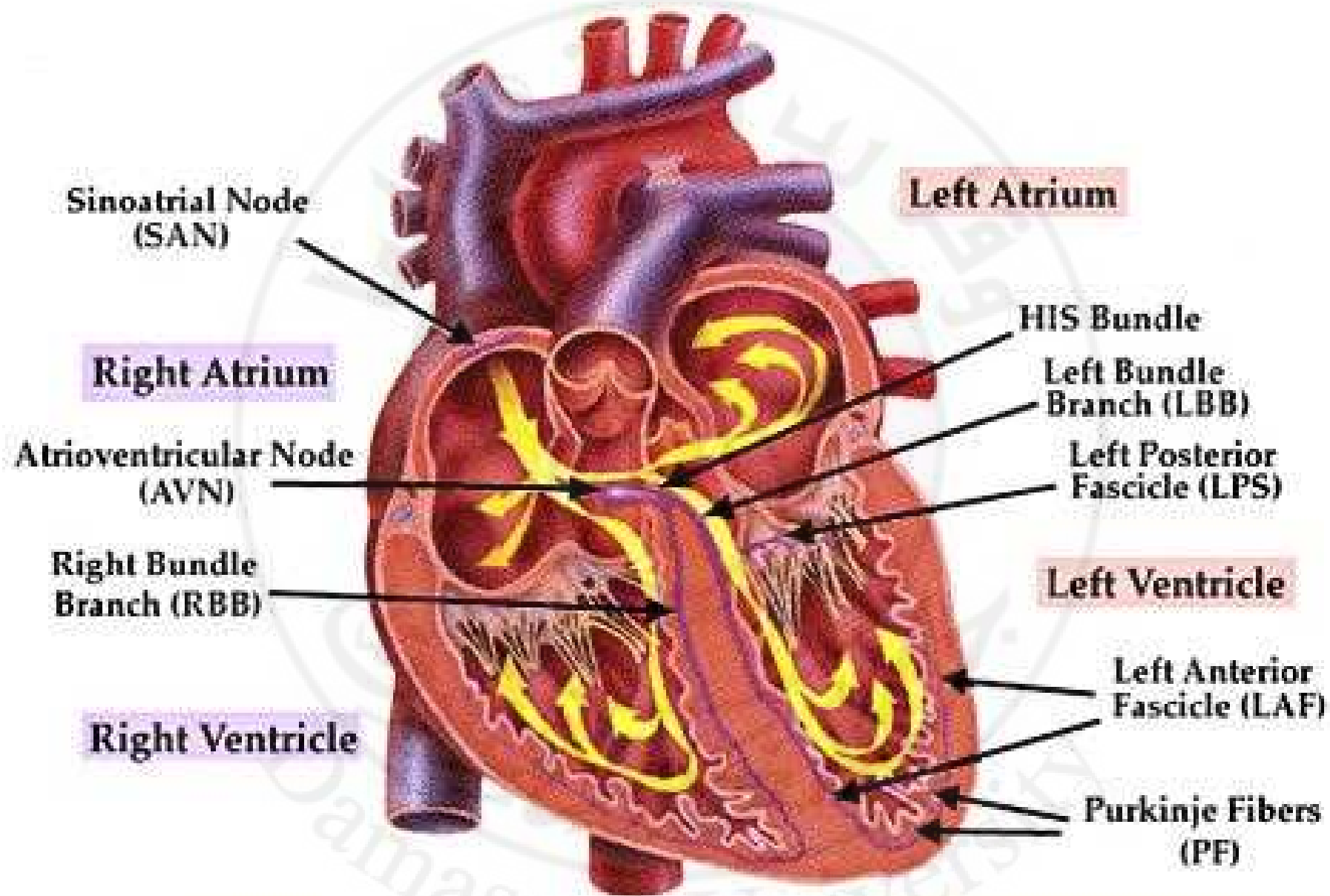


Anti arrhythmic Agents

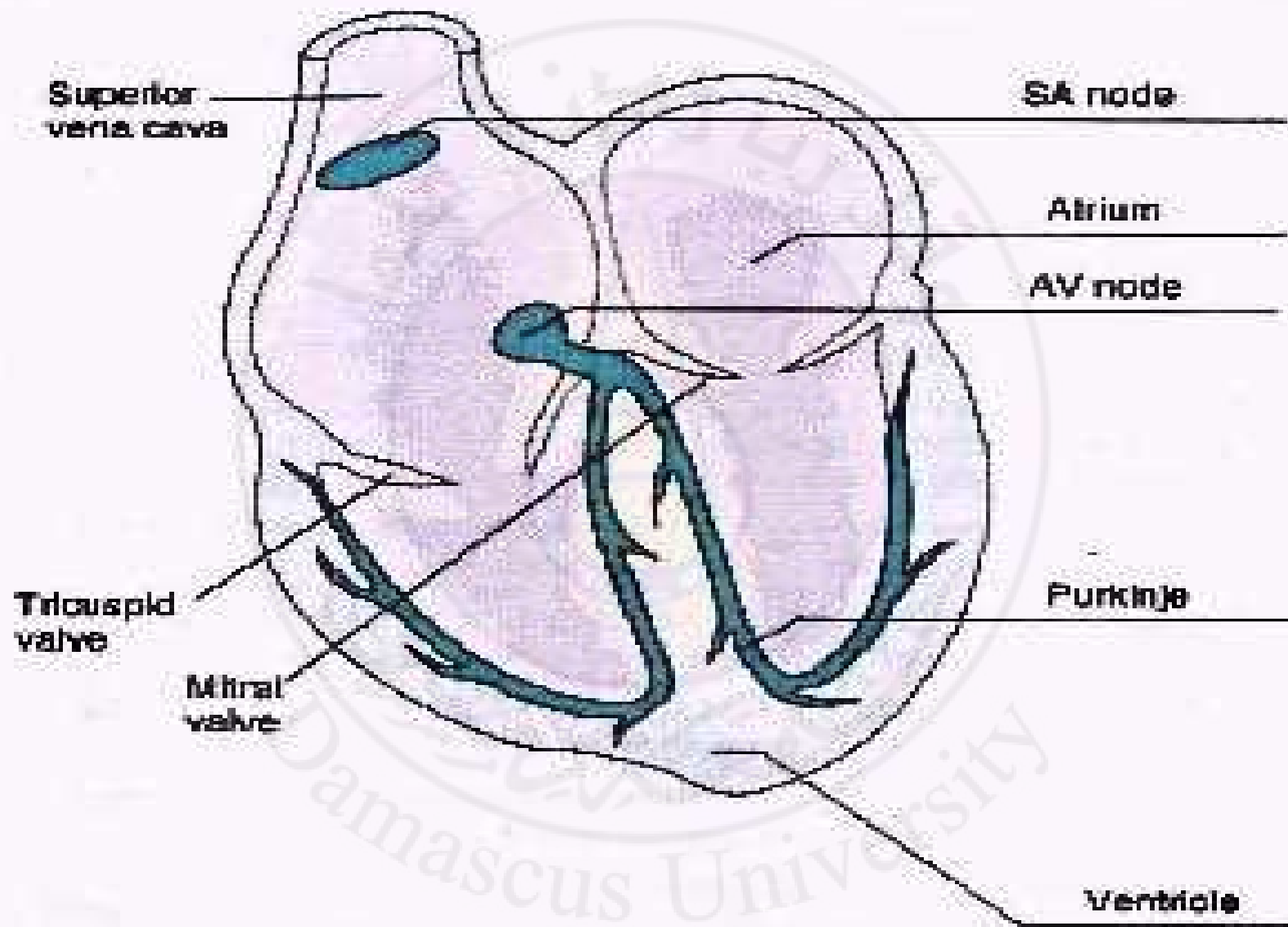


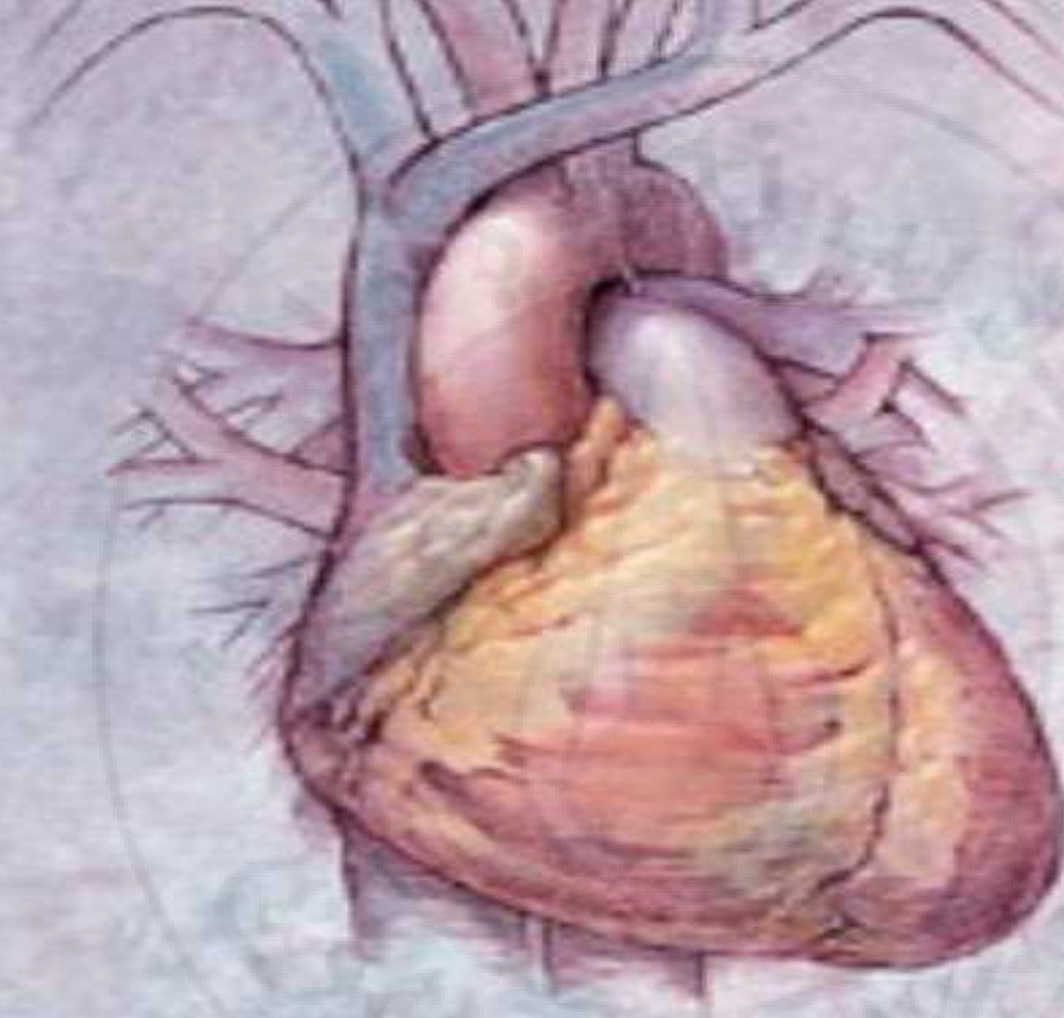
The sinoatrial node paces the heart by spontaneously depolarizing and stimulating the conducting nerves of the atrium. The impulse rapidly spreads through the atrium, causing myocardial cells of the atrium to contract in unison. The impulse reaches the atrioventricular (A-V) node, which in turn transmits the conduction signal to the His-Purkinje conduction pathway. The His-Purkinje system carries the impulse to ventricular myocardial cells, causing a powerful contraction that propels blood throughout the body.



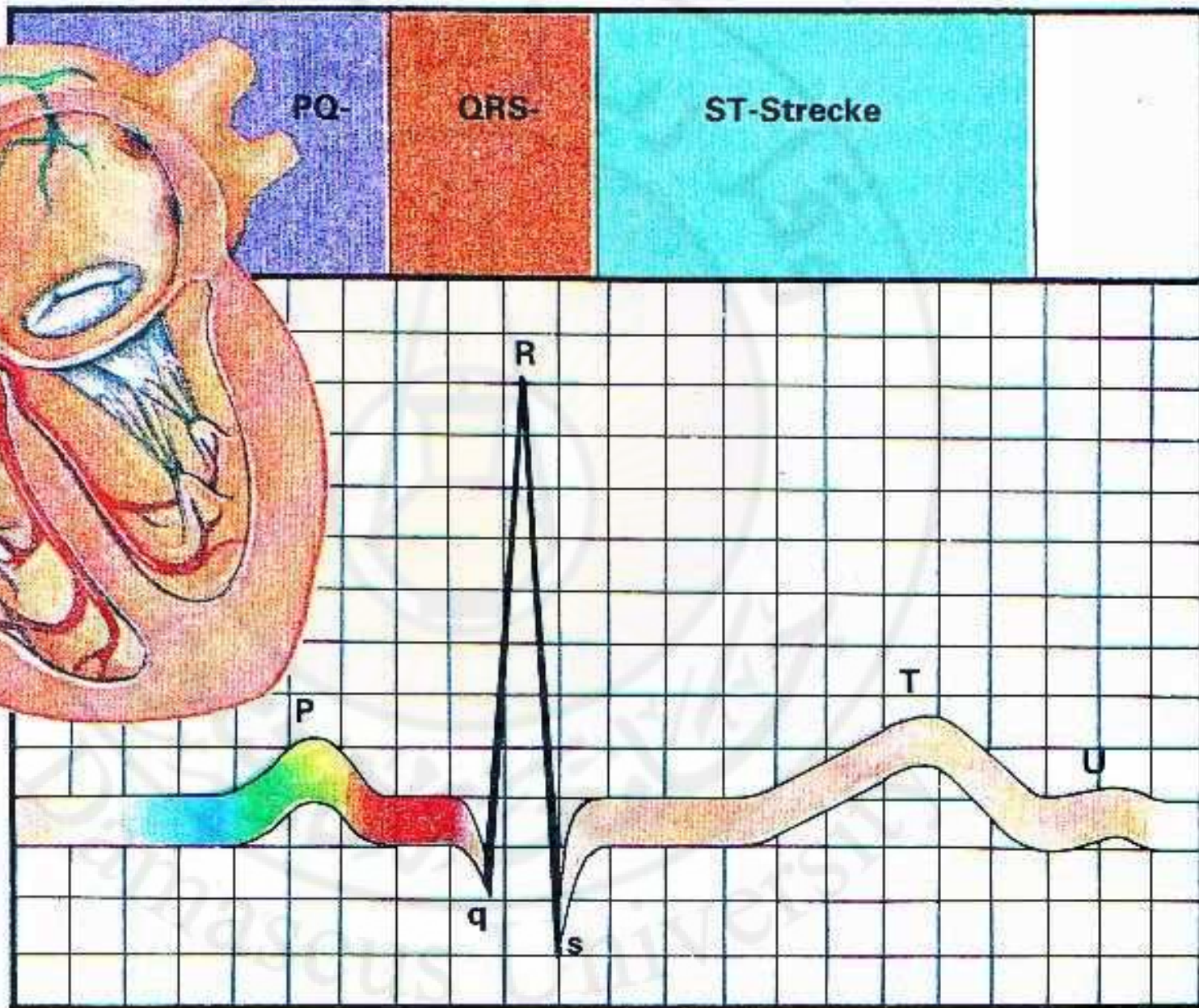
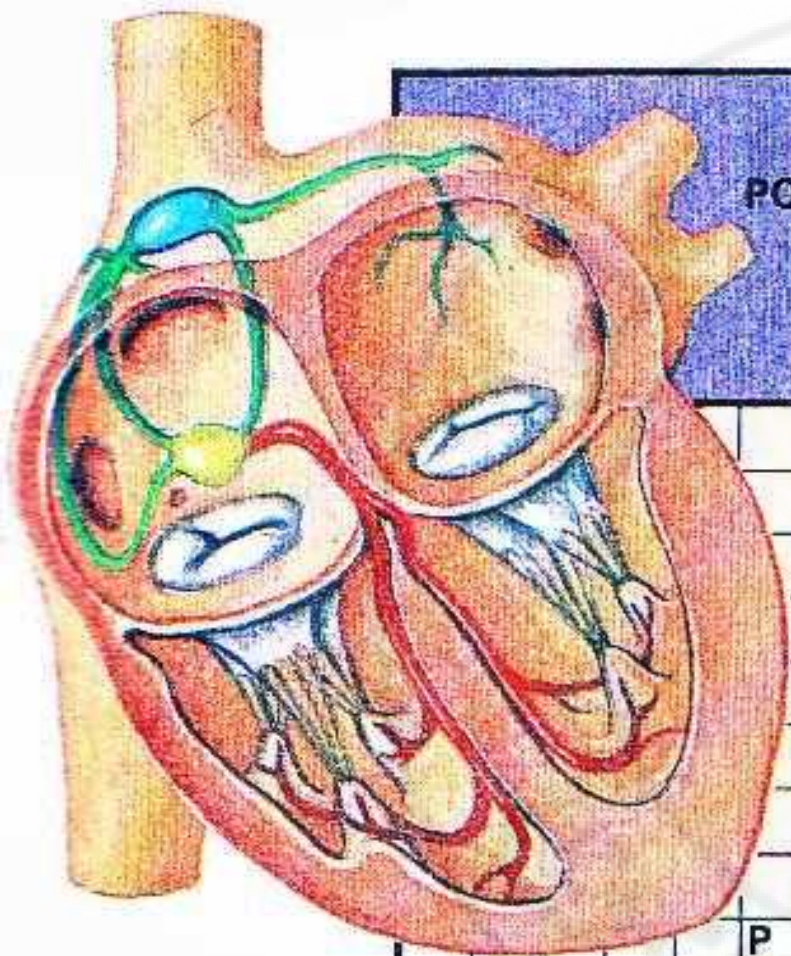


Cardiac Conduction System

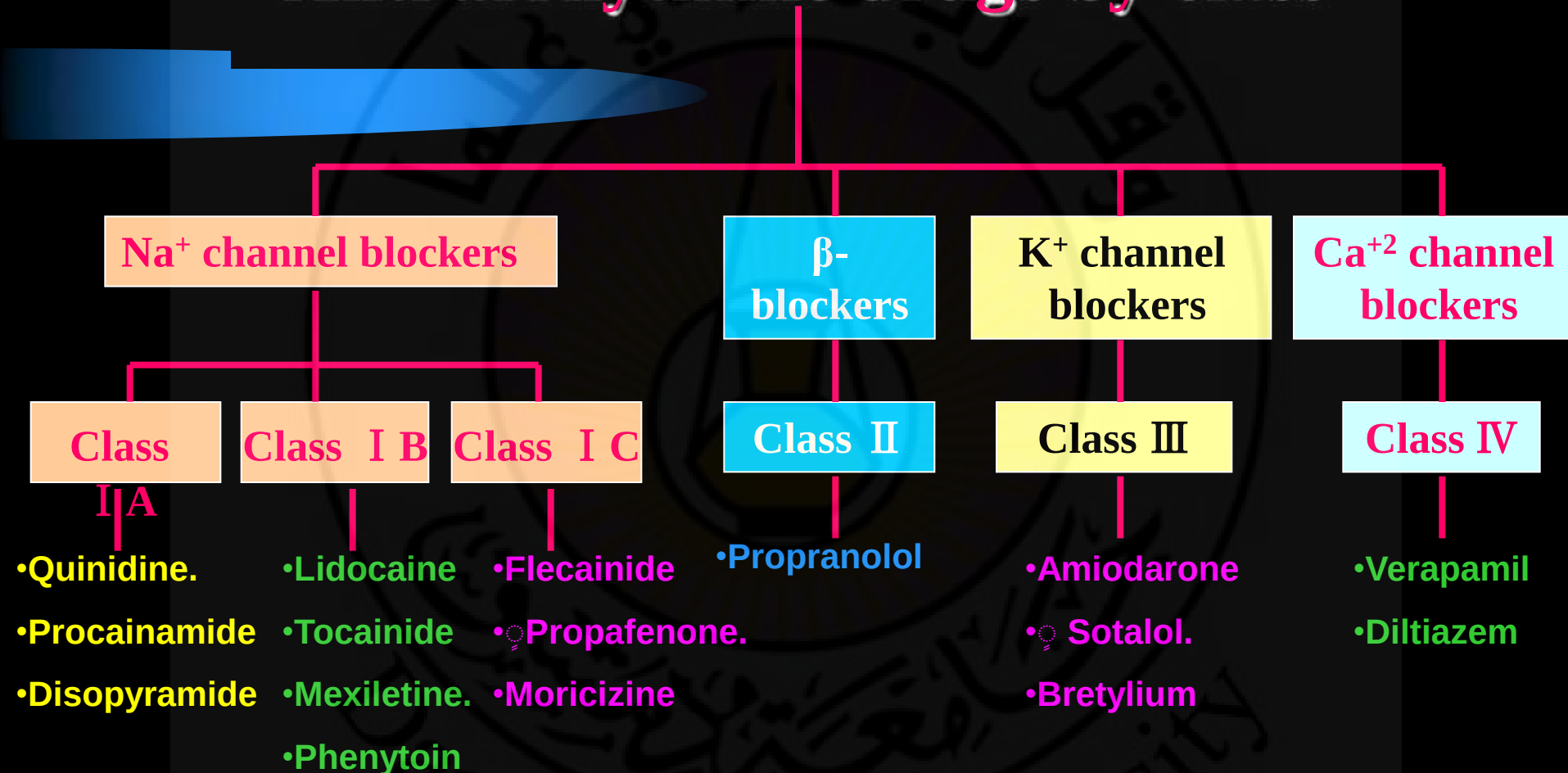




Organ	Effect of			
	Sympathetic		Parasympathetic	
	Action ¹	Receptor ²	Action	Receptor ²
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	...	...
Contractility	Increases	β_1, β_2	Decreases (atria)	$[M_2]$

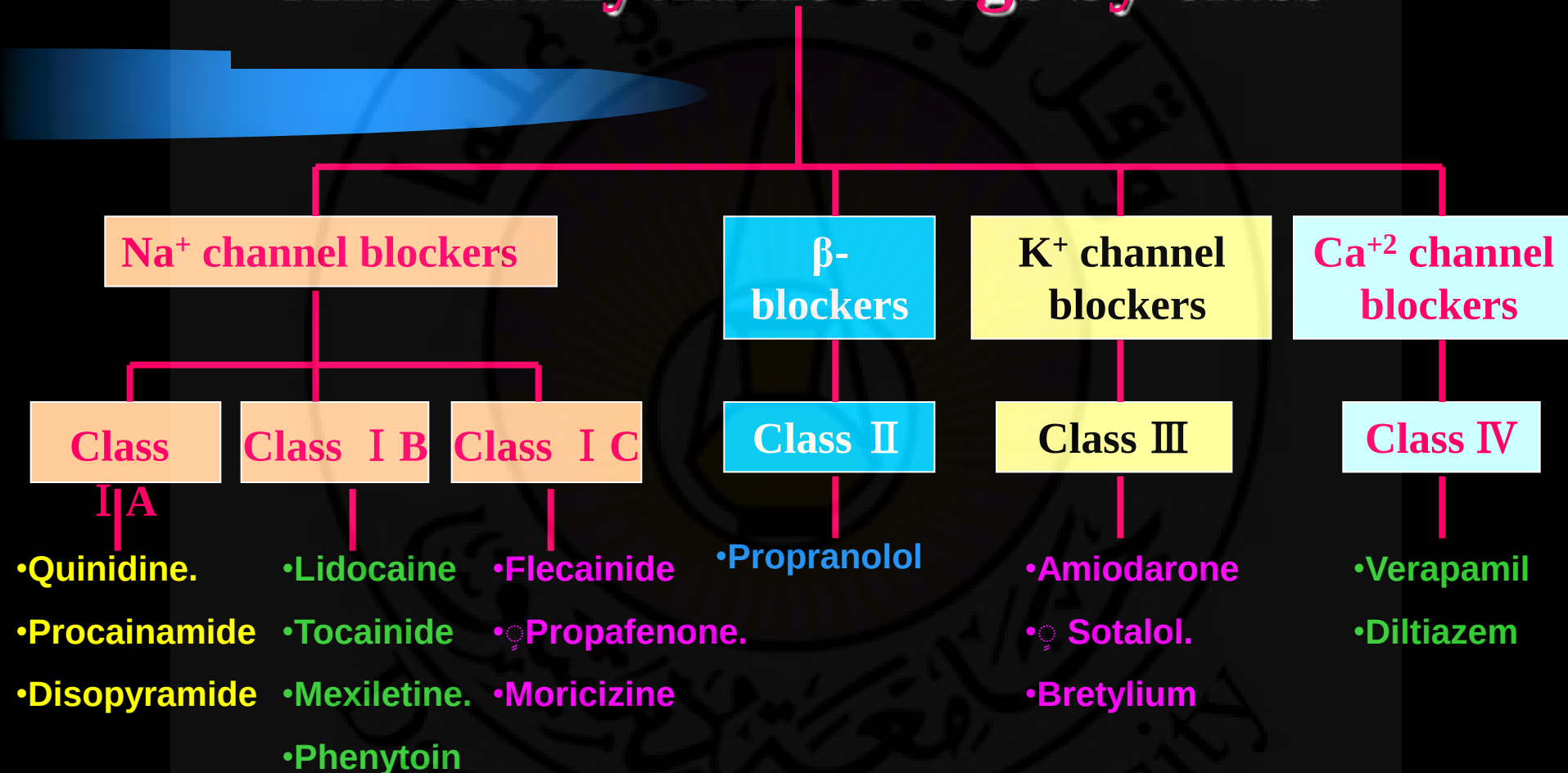


Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: **I, Sodium channel blockers**; **II, β- blockers**; **III, potassium channel blockers**, and **IV, Calcium channel blockers**

Pharmacokinetics

Quinidine

-  **A: PO and IV.**
-  **M: Hepatic metabolism.**
-  **E: Parent drug and metabolites excreted in urine.**

Pharmacokinetics

Procaïnamide

-  **A:** PO, IM, IV.
-  **M:** Hepatic metabolism to N- acetylprocainamide (NAPA).
-  **E:** in urine.

Pharmacokinetics

Disopyramide

-  **A: PO.**
-  **M: 50% hepatic metabolism.**
-  **E: Parent drug and metabolites excreted in urine.**

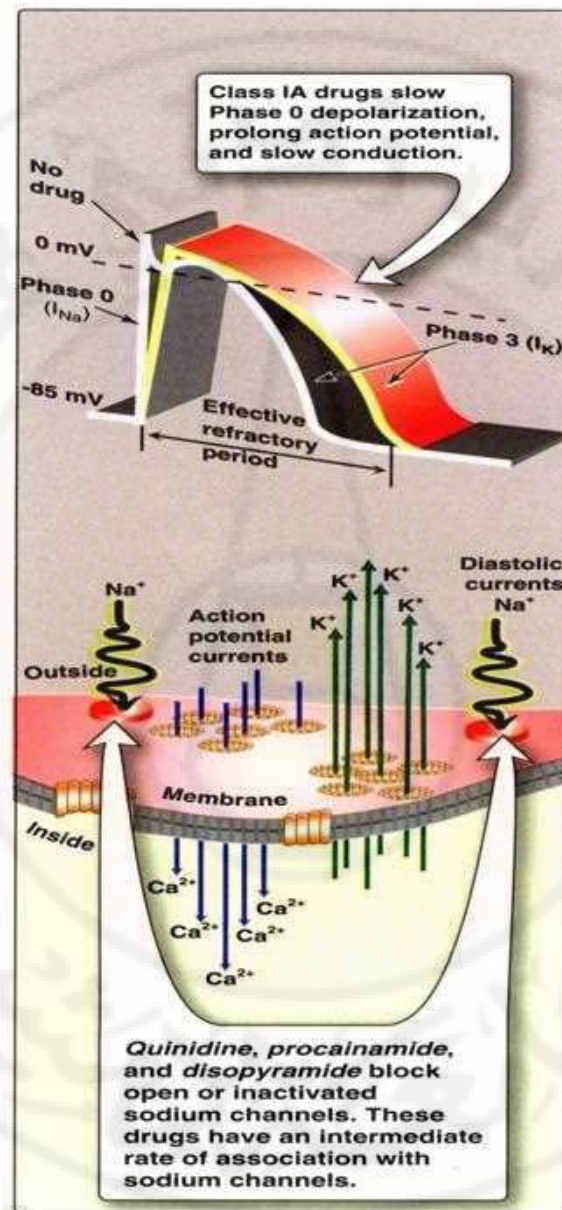


Figure 17.5

Schematic diagram of the effects of Class IA agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+ , respectively.

Mechanism of action

Quinidine, Procainamide & Disopyramide

- Inhibit fast Na^+ channel by blocking activated Na^+ channels.
- Weakly block K^+ channels (reduce repolarization), which increase AP duration (manifests as a lengthening of QT interval).

Clinical Uses



Quinidine

- ❖ All types of arrhythmias.
- ❖ Especially useful for atrial flutter, atrial fibrillation, and ventricular tachycardia

Clinical Uses



Procainamide

- ❖ Same as Quinidine .
- ❖ Especially useful for sustained ventricular arrhythmias associated with acute MI.

Clinical Uses

Disopyramide

❖ Ventricular arrhythmias.

Drawbacks and side effects

Quinidine

- ❖ Antimuscarinic activity can suppress vagal tone leading to an increase in A-V conduction, which may cause tachycardia and arrhythmias.
- ❖ Defective heteroregulatory decreased conduction can further lead to torsades de pointes and eventual quinidine syncope.
- ❖ Chinchonism.
- ❖ GI symptoms (nausea, vomiting, diarrhea).
- ❖ Digitalis toxicity: quinidine increase plasma digoxin levels.

The most common side effects of quinidine are diarrhea, nausea, headache, and dizziness. These side effects make it difficult for patients to tolerate chronic therapy with quinidine. Quinidine is contraindicated in patients with QT prolongation and in patients who are taking medications that predispose to QT prolongation, because of the increased risk of *torsades de pointes*. Relative contraindications to quinidine use include sick sinus syndrome, bundle branch block, myasthenia gravis (because of quinidine's antagonist action at muscarinic receptors), and liver failure.

Drawbacks and side effects

Procainamide

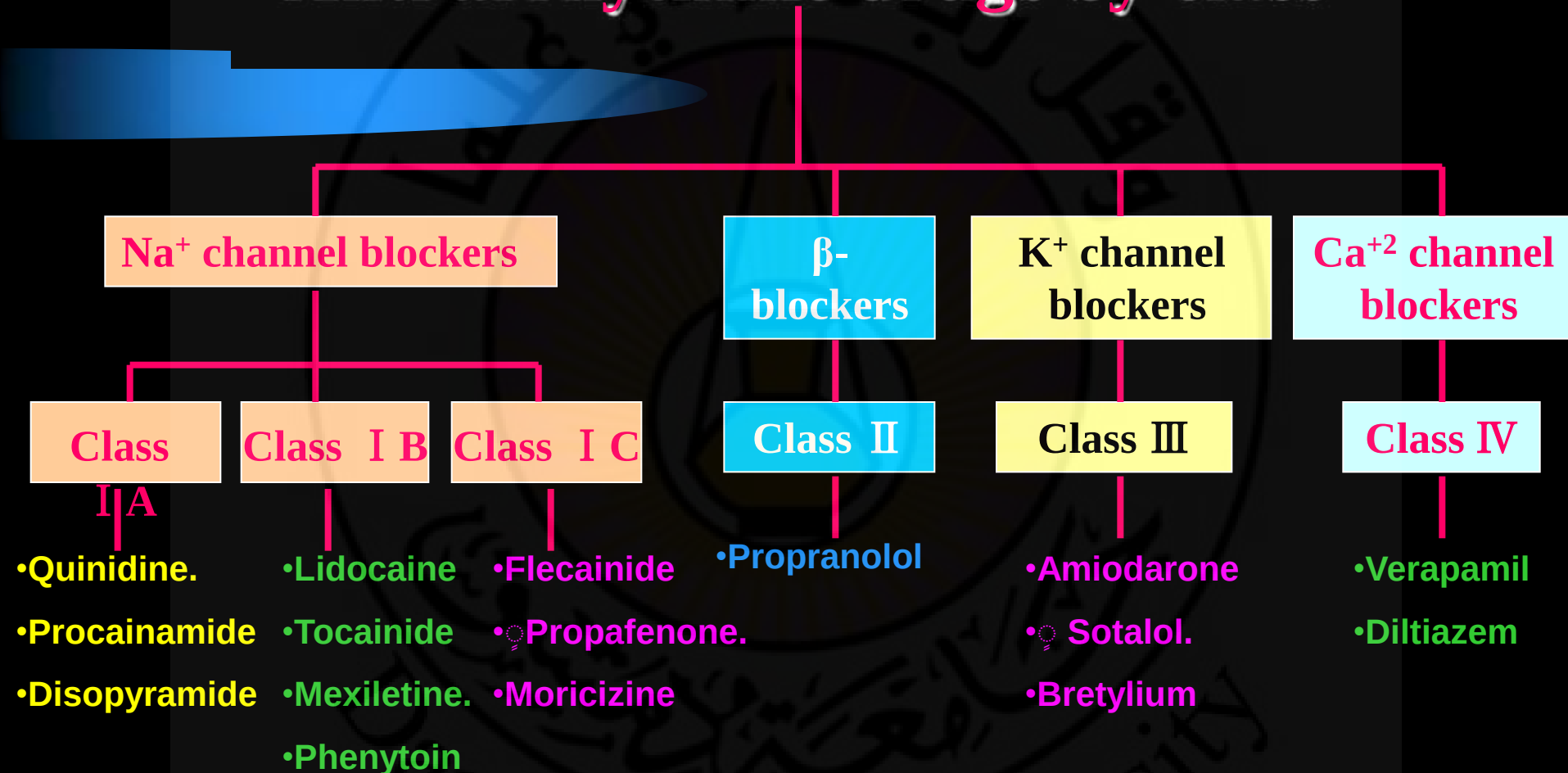
- ❖ GI symptoms (nausea, vomiting).
- ❖ Hypotension.
- ❖ I TII can lead to lupus – like syndrome via unknown mechanism.
- ❖ Torsades de pointes.

Drawbacks and side effects

Disopyramide

- ❖ Antimuscarinic activity can suppress vagal tone leading to an increase in A/V conduction, which may cause tachycardia and arrhythmias.
- ❖ Negative inotropic effects may precipitate failure in patients with ventricular dysfunction.
- ❖ **Antimuscarinic Side effects.**
- ❖ Torsades de pointes.

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers

Pharmacokinetics

Lidocaine

 **A: IV, IM.**

 **M: Hepatic metabolism.**

 **E: Parent drug and metabolites excreted in urine.**

Pharmacokinetics

Tocainide

 **A: PO**

 **E: Unchanged in urine.**

Pharmacokinetics

Mexiletine

 **A: PO.**

 **M: 90% metabolized to inactive metabolites.**

 **E: Parent drug and metabolites excreted in urine.**

Pharmacokinetics

Phenytoin

-  **A: PO and IV.**
-  **M: Partial hepatic metabolism.**
-  **E: Parent drug and metabolites excreted in urine.**

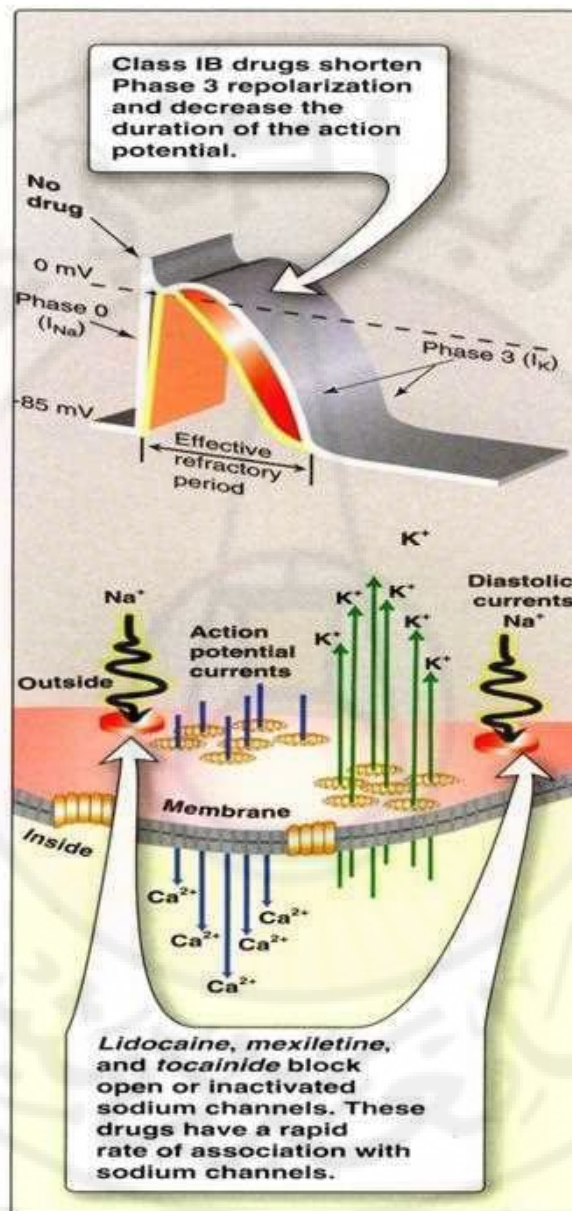


Figure 17.6
Schematic diagram of the effects of Class IB agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+ , respectively.



Mechanism of action

- ❖ *Inhibit both inactive and active Na^{+2} channels.*
- ❖ *Act preferentially on depolarized, arrhythmogenic tissue.*
- ❖ *Shorten AP duration.*

Clinical Uses



Lidocaine

- ❖ **Suppression of recurrent ventricular tachycardia and fibrillation.**

Clinical Uses



**Tocainide
&
Mexiletine**

❖ **Ventricular
arrhythmias.**

Clinical Uses



Phenytoin

❖ **Ventricular
tachycardia and
paroxysmal atrial
tachycardia.**



❖ Lidocaine

- **CNS side effects (tremor, light – headedness, nausea of central origin, paresthesias).**



❖ Tocainide & Mexiletine

- GI side effects (nausea).
- Neurologic side effects
(tremor, lethargy, blurred vision)

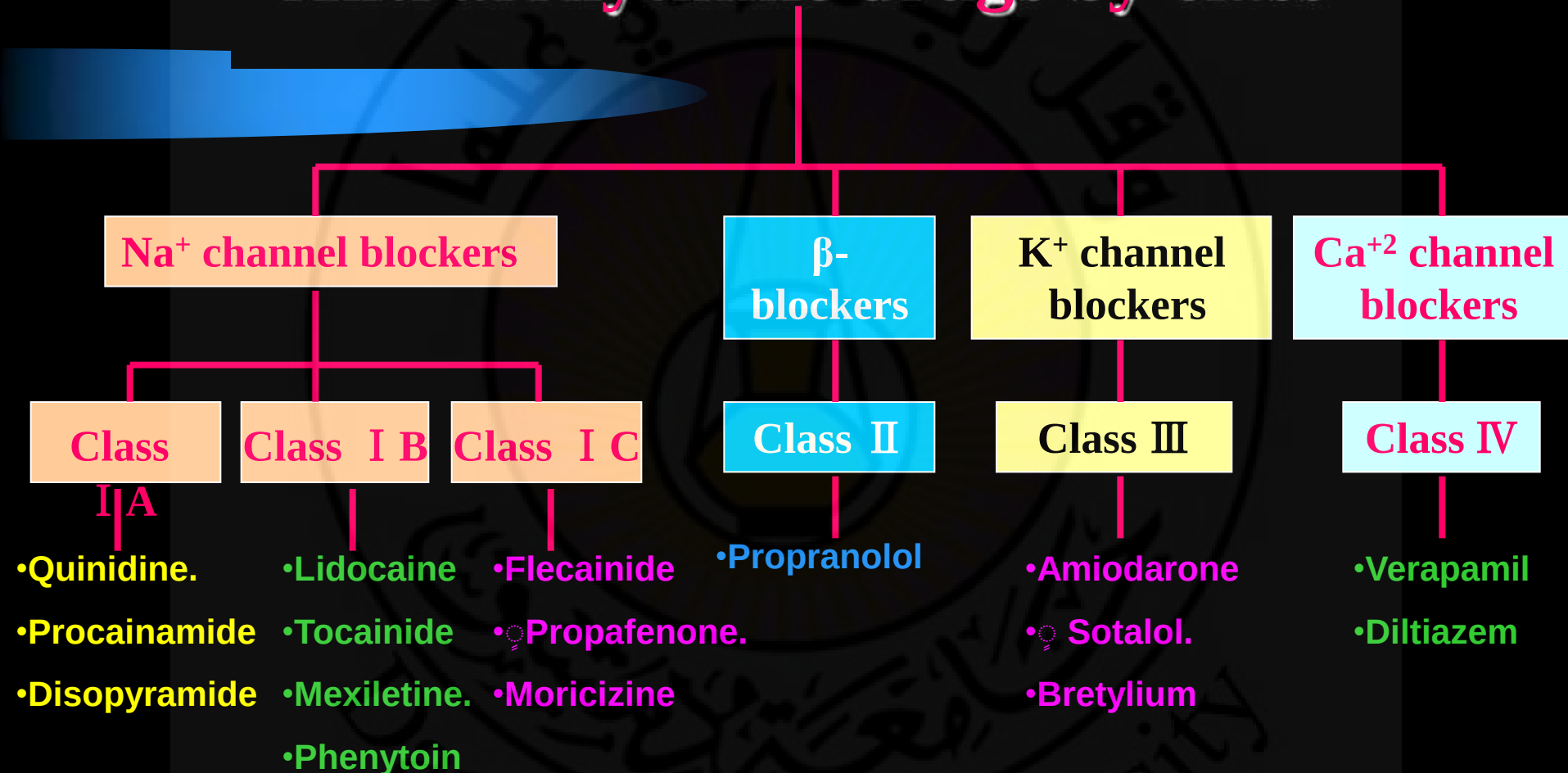
Damascus University



❖ Phenytoin

- Hypotension.
- Vertigo.
- Lethargy.
- Gingivitis.
- Lupus.
- Pulmonary infiltrates.

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers

Pharmacokinetics

Flecainide

-  **A:** PO and IV; well absorbed.
-  **M:** Hepatic metabolism to inactive metabolites .
-  **E:** Parent drug and metabolites excreted in urine.

Pharmacokinetics

Propafenone

-  **A:** PO and IV.
-  **M:** Hepatic metabolism.
-  **E:** Parent drug and metabolites mainly excreted in feces.

Pharmacokinetics

Moricizine

-  **A:** PO.
-  **M:** Hepatic metabolism.
-  **E:** Metabolites excreted in urine.

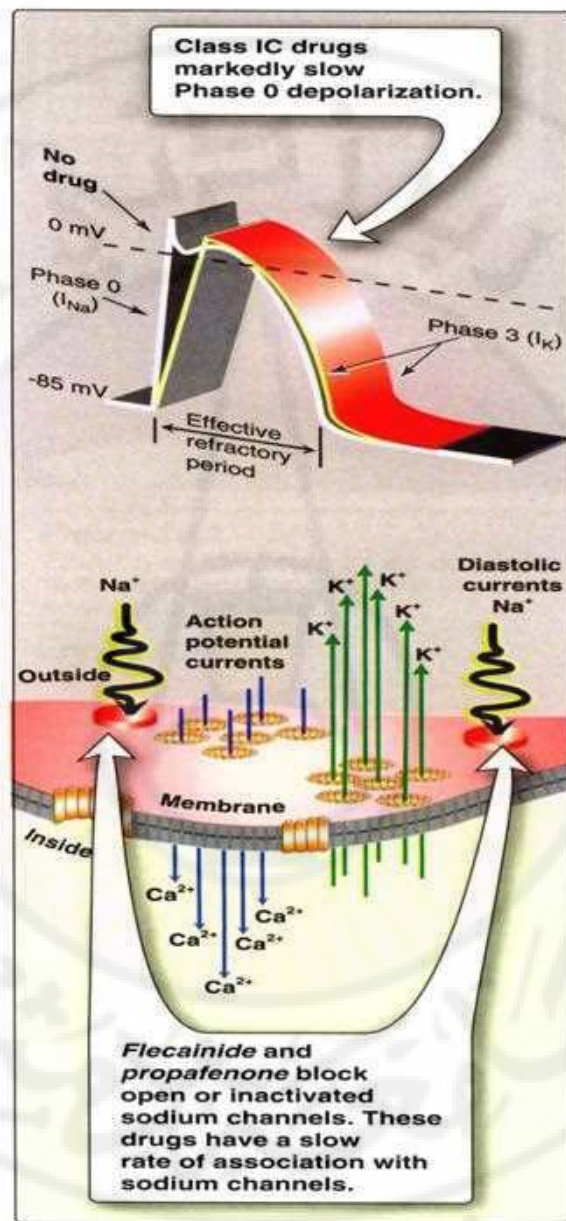
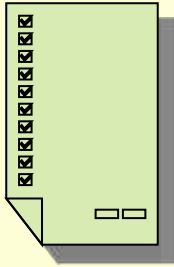
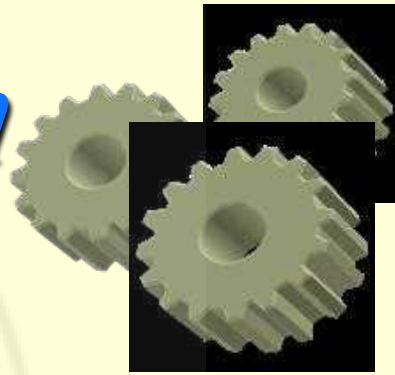


Figure 17.7

Schematic diagram of the effects of Class IC agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+ , respectively.



Mechanism of action

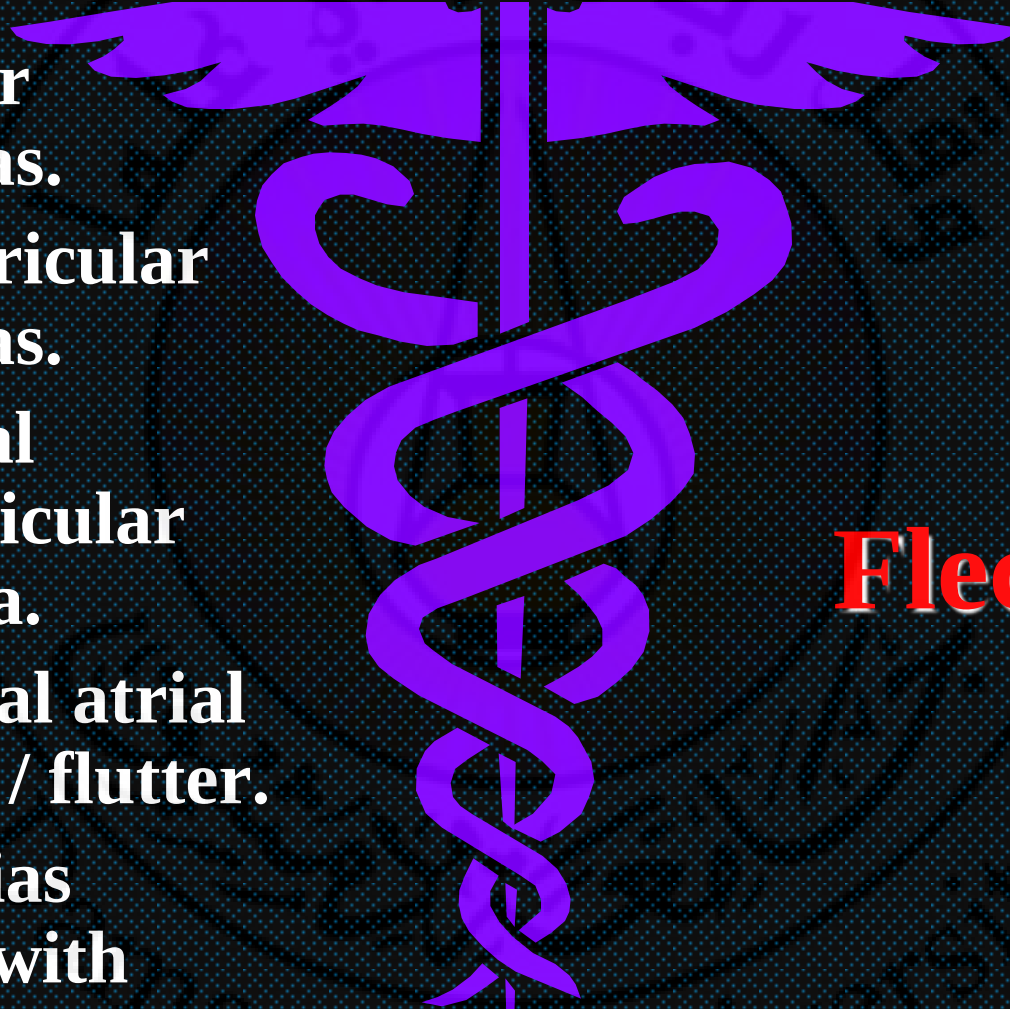


- **Inhibit fast Na^+ channels.**
- **Especially effective in the His – Purkinje system (widens QRS complex)**
- **Usually little effective on AP duration.**

Clinical Uses

- ❖ Ventricular arrhythmias.
- ❖ Supraventricular arrhythmias.
- ❖ Paroxysmal supraventricular tachycardia.
- ❖ Paroxysmal atrial fibrillation / flutter.
- ❖ Arrhythmias associated with Wolff – Parkinson-White syndrome.

Flecainide



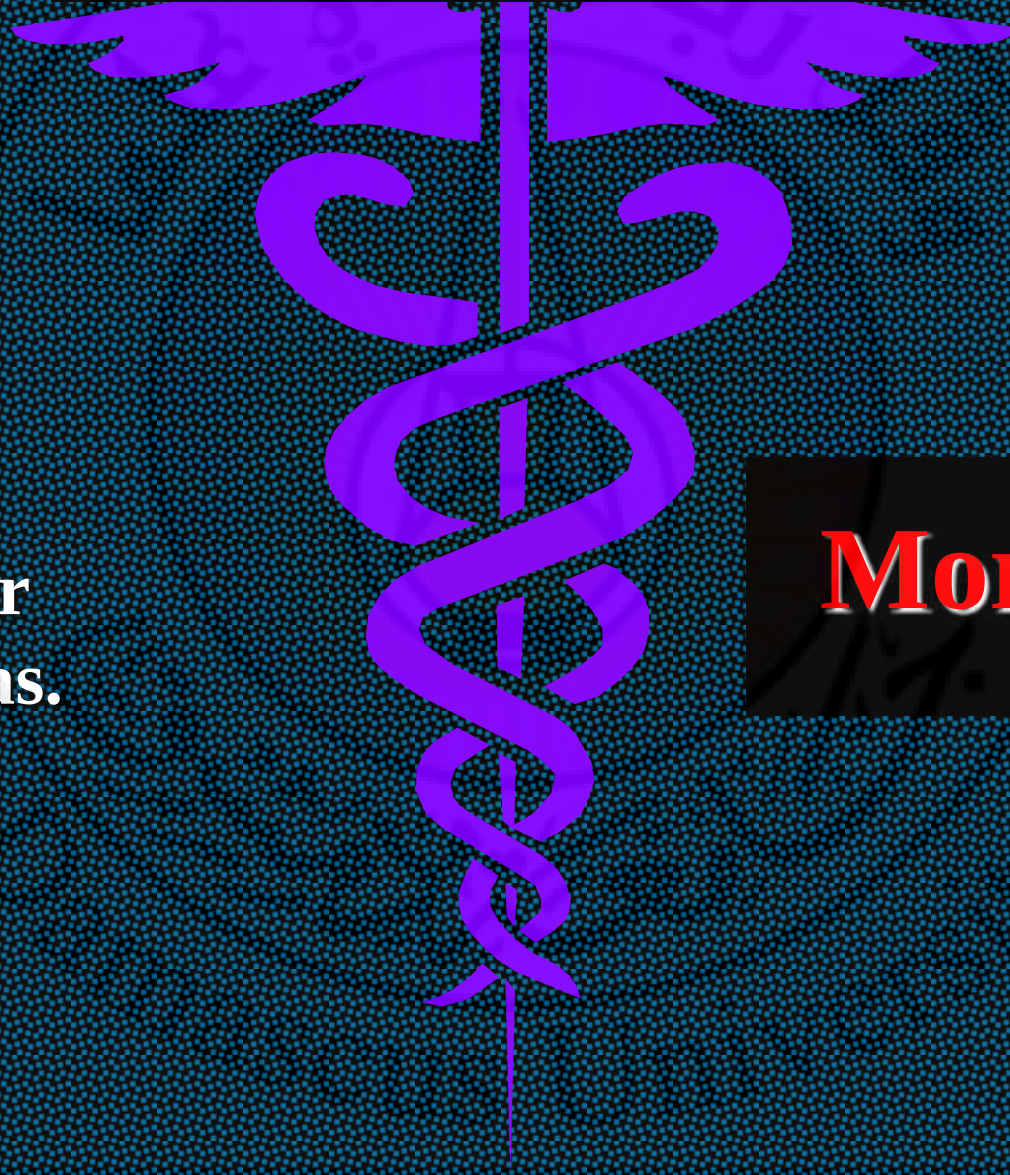
Clinical Uses



❖ Supraventricular
arrhythmias.

Propafenone

Clinical Uses



Moricizine

❖ Ventricular
arrhythmias.

Drawbacks and Side effects

Flecainide

- ✚ *Prolongation of QRS complex.*
- ✚ *Proarrhythmic.*
- ✚ *CNS side effects.*

Drawbacks and Side effects

Propafenone

- *Metallic taste.*
- *Constipation.*
- *Prolongation of QRS interval*
- *Proarrhythmia.*
- *GI side effects.*

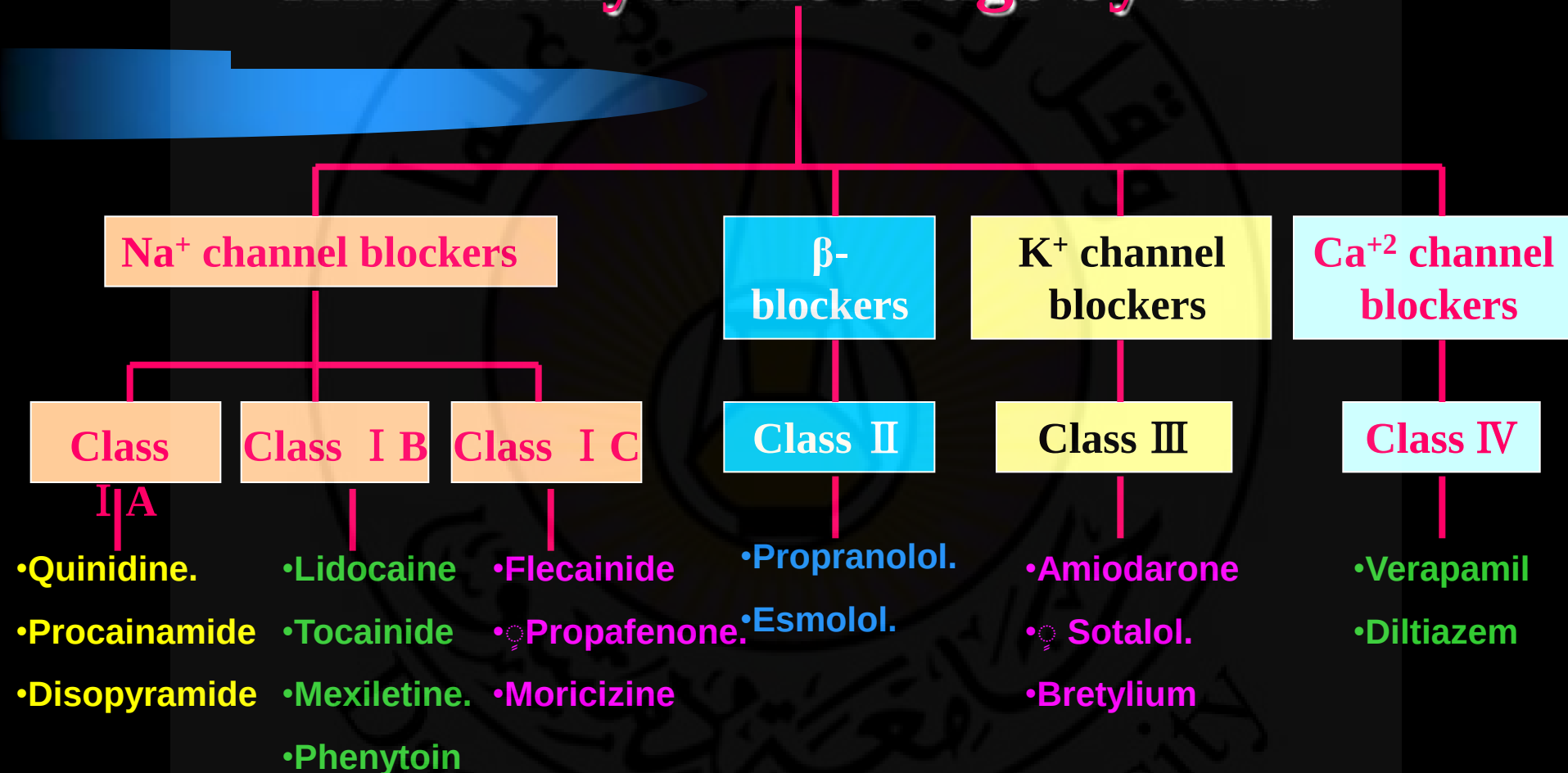
Drawbacks and Side effects

Moricizine

 *dizziness.*

 *Nausea.*

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers



❖ *Pharmacokinetics:*

✓ *A: IV or PO.*

❖ *Mechanism of action:*

✓ *block sympathetic effects on the heart.*

✓ *Affect primarily the SA and AV nodes.*

✓ *Decrease SA node automaticity and AV nodal conduction.*

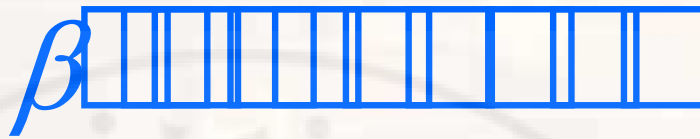


❖ *Clinical Uses*

- ✓ *Supraventricular arrhythmias.*
- ✓ *Control of ventricular rate during atrial flutter and fibrillation.*

❖ *Side effects:*

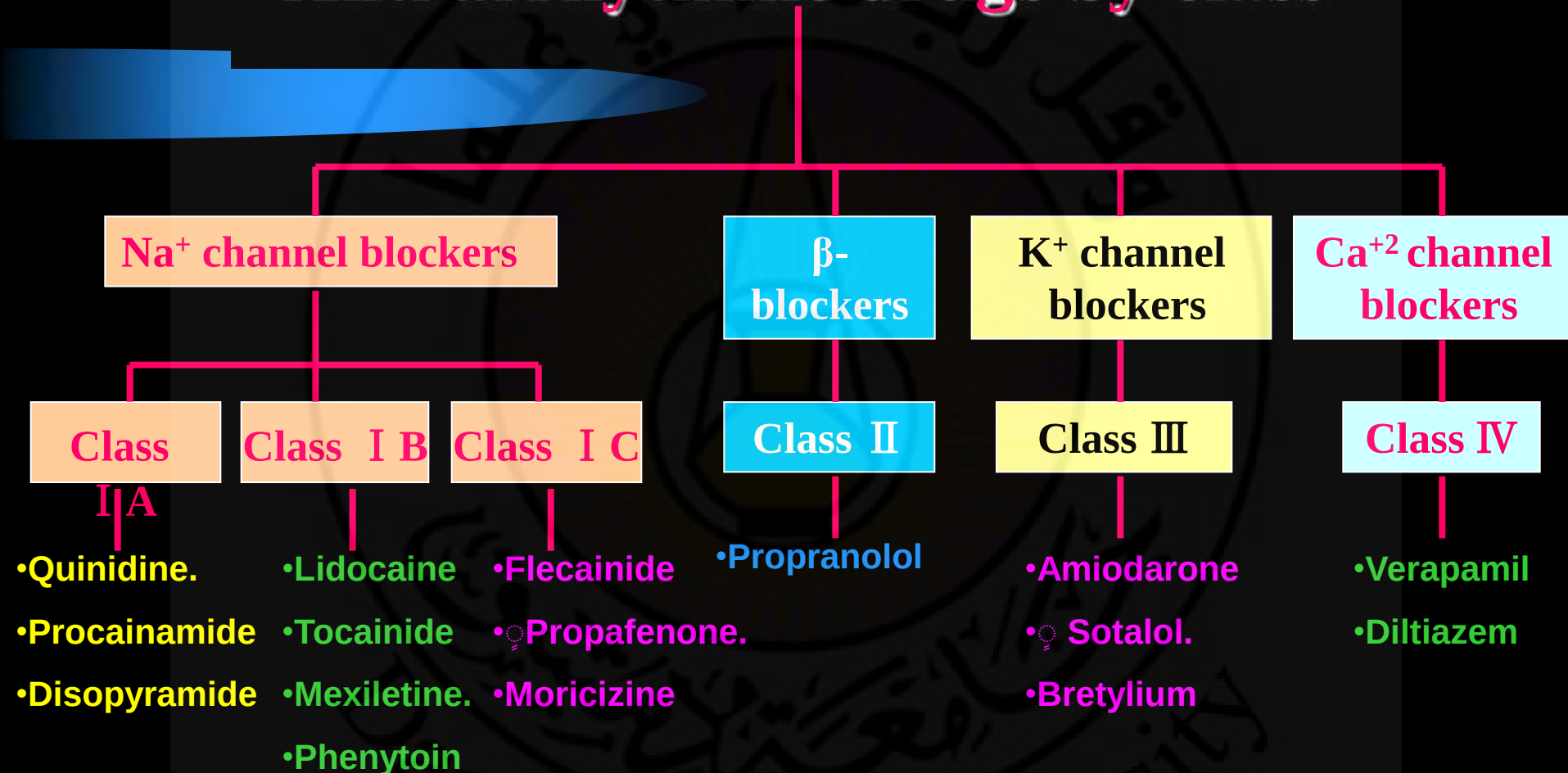
- ✓ *Contraindicated in asthmatic patients (bronchoconstriction).*
- ✓ *Sudden withdrawal can lead to rebound hypersensitivity, node automaticity and A/V nodal conduction.*



➤ Esmolol

- ❖ β_1 adrenergic receptor- preferring antagonist. Similar to propranolol in action.
- ❖ Less likely to cause bronchospasm than propranolol. Otherwise similar.
- ❖ Metabolized by erythrocyte esterase. Metabolite excreted renally. Serum levels unaffected by liver or kidney failure.
- ❖ No significant interactions with digoxin.

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers

Pharmacokinetics

Amiodarone

- **A:** *IV and PO; slow GI absorption; long period to reach steady state.*
- **M:** *Hepatic metabolism to active metabolite.*
- **E:** *Excreted by lacrimal glands, skin, and biliary tract.*

Pharmacokinetics

Bretylium

 **A:** *IM and IV.*

 **E:** *Unchanged in urine.*



Sotalol

 **A:** *PO; well absorbed.*

 **E:** *Unchanged in urine.*

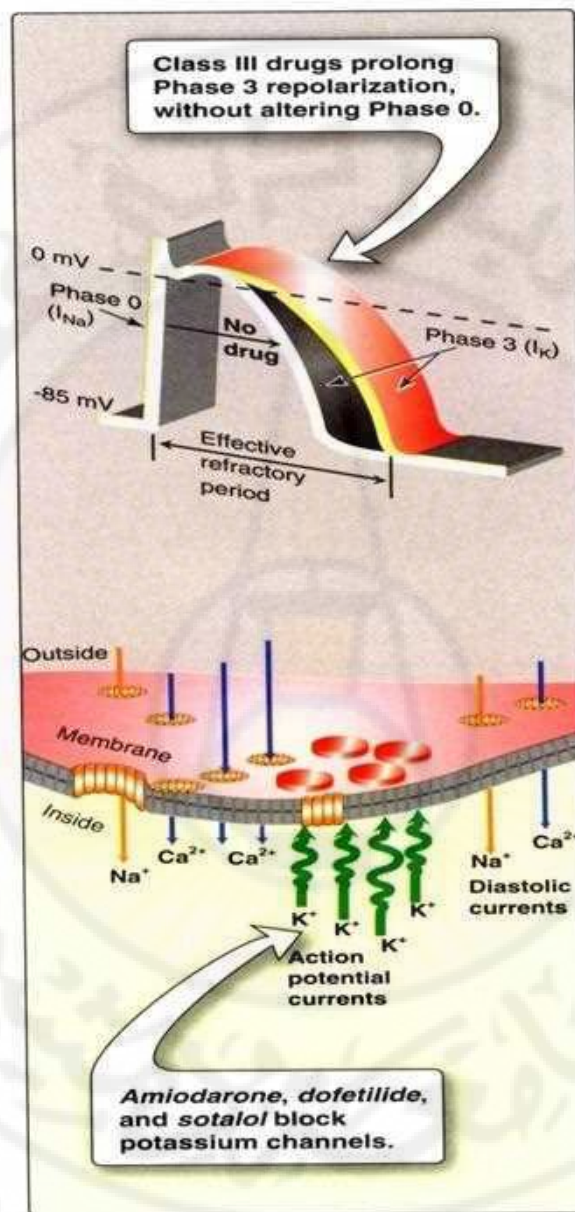


Figure 17.8

Schematic diagram of the effects of Class III agents. I_{Na} and I_{K} are transmembrane currents due to the movement of Na^+ and K^+ , respectively.

Mechanism of action

Amilorone

- Prolongs AP duration by blocking K^+ channels.
- Does not effect conduction velocity.
- Blocks Na^+ channels.
- Blocks calcium channels.
- Some β - blocker activity.
- Coronary and peripheral vasodilator.

Mechanism of Action

Sotalolol

&

Bretium

➤ Prolongs AP duration.

➤ Possesses β - blocker and potassium- channel blocking activity.

➤ Same as Amiodarone.

➤ Blocks the release of catecholamines from nerves after initial stimulation of release.

Clinical Uses

- ❖ Ventricular tachyarrhythmias.
(especially in post MI and CHF patients).
- ❖ Atrial fibrillation / flutter.
- ❖ Paroxysmal supraventricular tachycardia
- ❖ Arrhythmias associated with Wolff – Parkinson-White syndrome.
- ❖ Ventricular arrhythmias.
(especially in post MI patients).

Amiodarone

Sotalol

&

Bretylium

Drawbacks and Side effects

Amiodarone

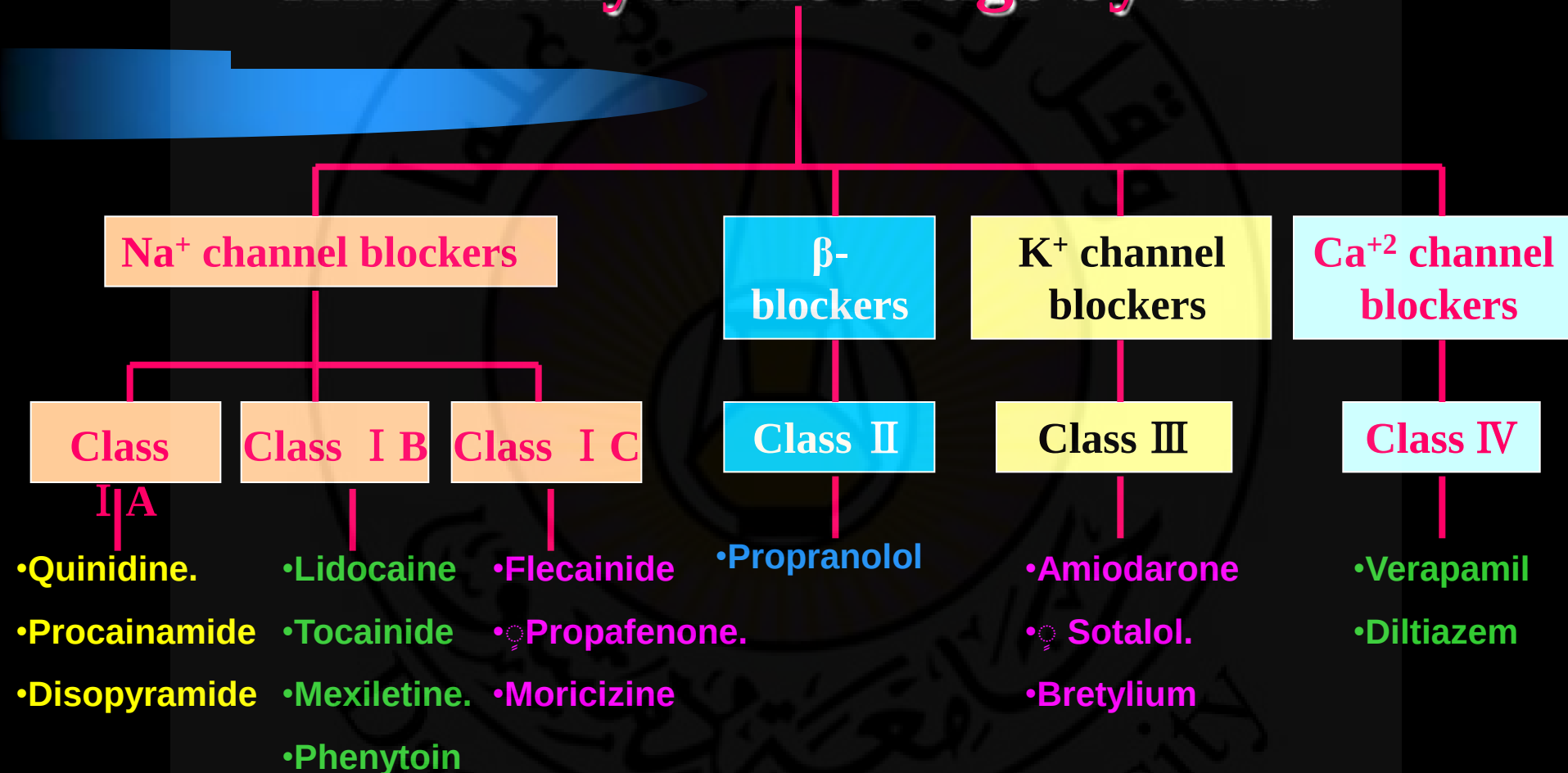
- *Pulmonary fibrosis.*
- *Hypothyroidism or hyperthyroidism.*
- *Paresthesias/ tremor.*
- *Torsades de points.*

Drawbacks and Side effects

Sotalol & Bretylium

- *Bradycardia.*
- *Bronchospasm.*
- *Fatigue.*
- *Torsades de points.*
- *Hypotension.*
- *Sympathomimetic effects.*

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers

Pharmacokinetics

Verapamil

-  **A:** PO and IV.
-  **M:** Extensive first - pass hepatic metabolism; metabolized by P450 enzymes to active metabolite.
-  **E:** Metabolites excreted in urine and feces.

Diltiazem

-  **A:** PO and IV.
-  **M:** Extensive first - pass hepatic metabolism; metabolized by P450 enzymes to less active metabolites.
-  **E:** in urine and feces.

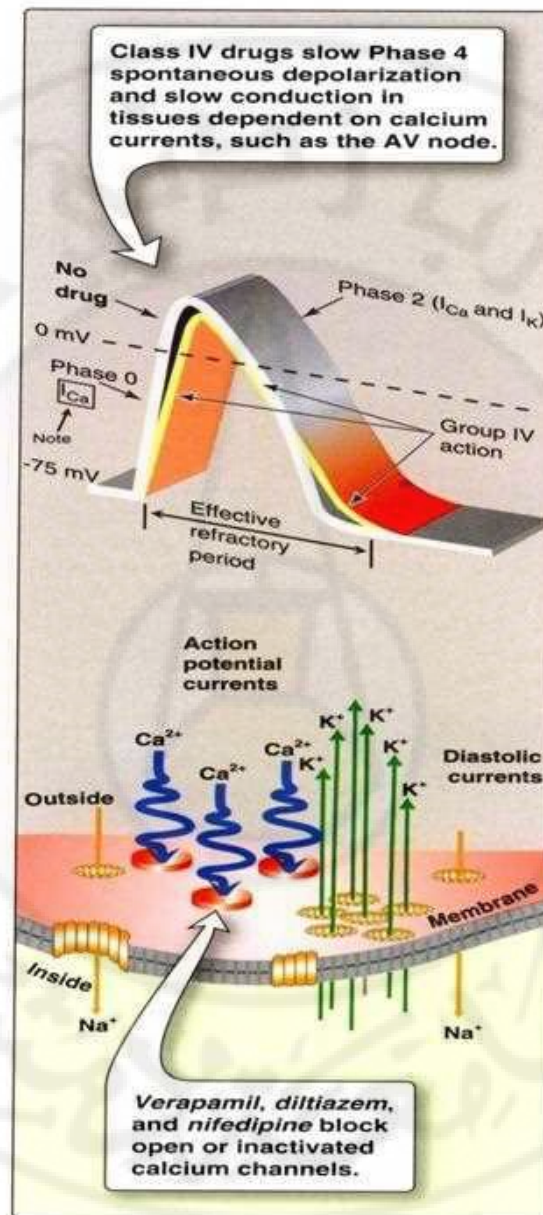
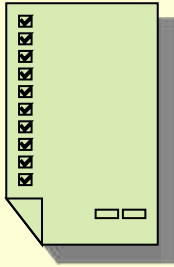
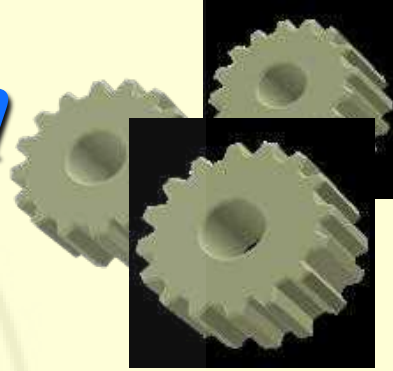


Figure 17.10

Schematic diagram of the effects of Class IV agents. I_{Ca} and I_K are transmembrane currents due to the movement of Ca^{2+} and K^+ , respectively.



Mechanism of action



- **Calcium channel blocker that effects mainly the SA and AV nodes.**
- **Reduces SA node automaticity and AV nodal conduction.**

Clinical Uses



**Verapamil
&
Diltiazem**

- ❖ **Supraventricular arrhythmias.**
- ❖ **Ventricular rate control in atrial flutter and fibrillation.**

Side effects

Verapamil

- ❖ **Contraindicated with β - blockers.**
- ❖ **Bradycardia.**
- ❖ **Constipation.**
- ❖ **Decreased cardiac contractility.**
- ❖ **Hypotension.**
- ❖ **Lassitude.**
- ❖ **Nervousness.**
- ❖ **Peripheral edema**

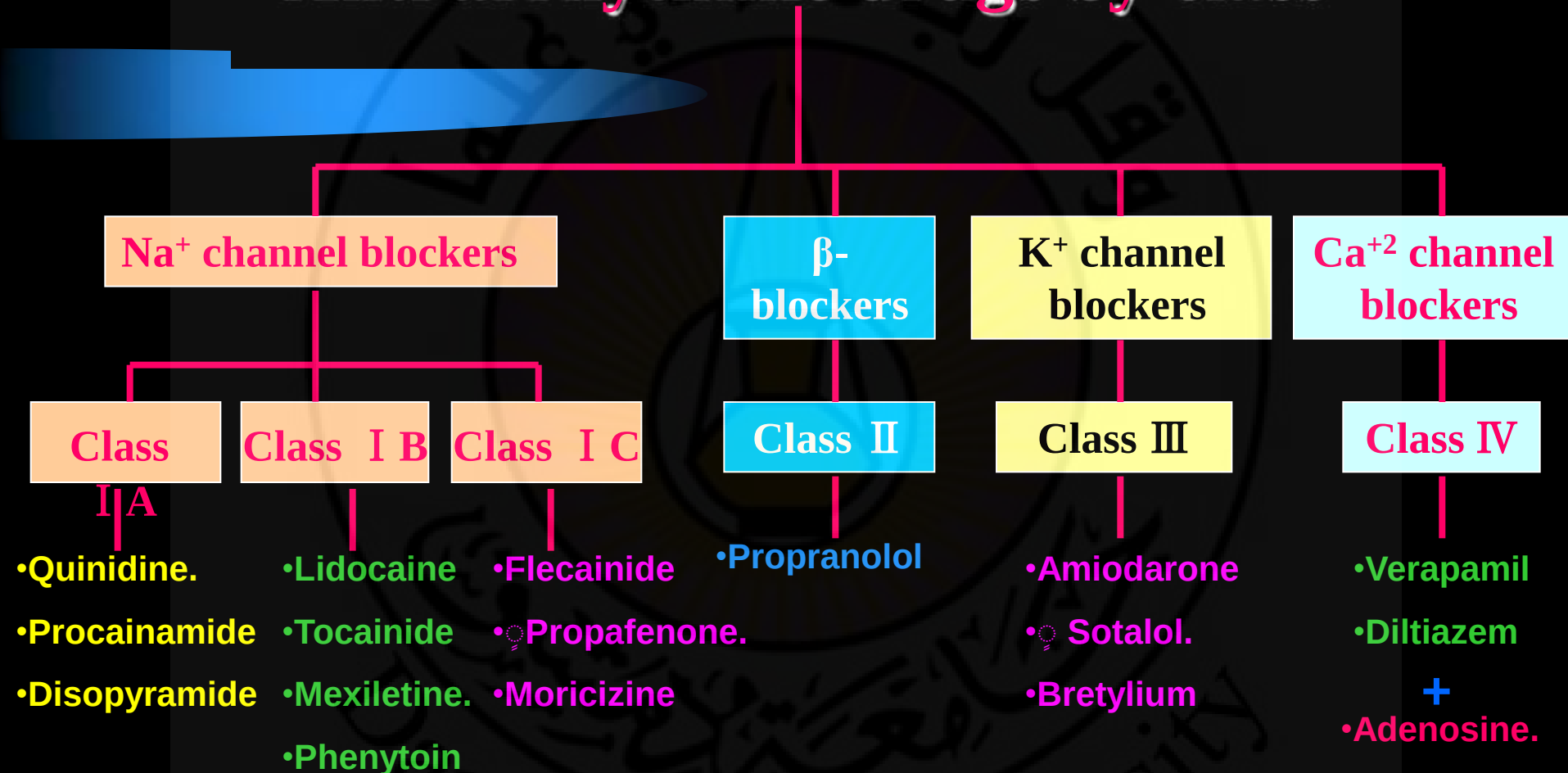
Side effects



Diltiazem

- ❖ **Bradycardia.**
- ❖ **Decreased cardiac contractility.**
- ❖ **Hypotension.**

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers

Adenosine

Pharmacokinetics

☒ Rapidly (<30 seconds) deaminated in serum to active agent, inosine.

Adenosine

Mechanism of action

✕ Decrease conduction velocity, prolong refractory period and decreases automaticity in A-V nod

Adenosine

Clinical Uses

✕ Paroxysmal supraventricular tachyarrhythmias.

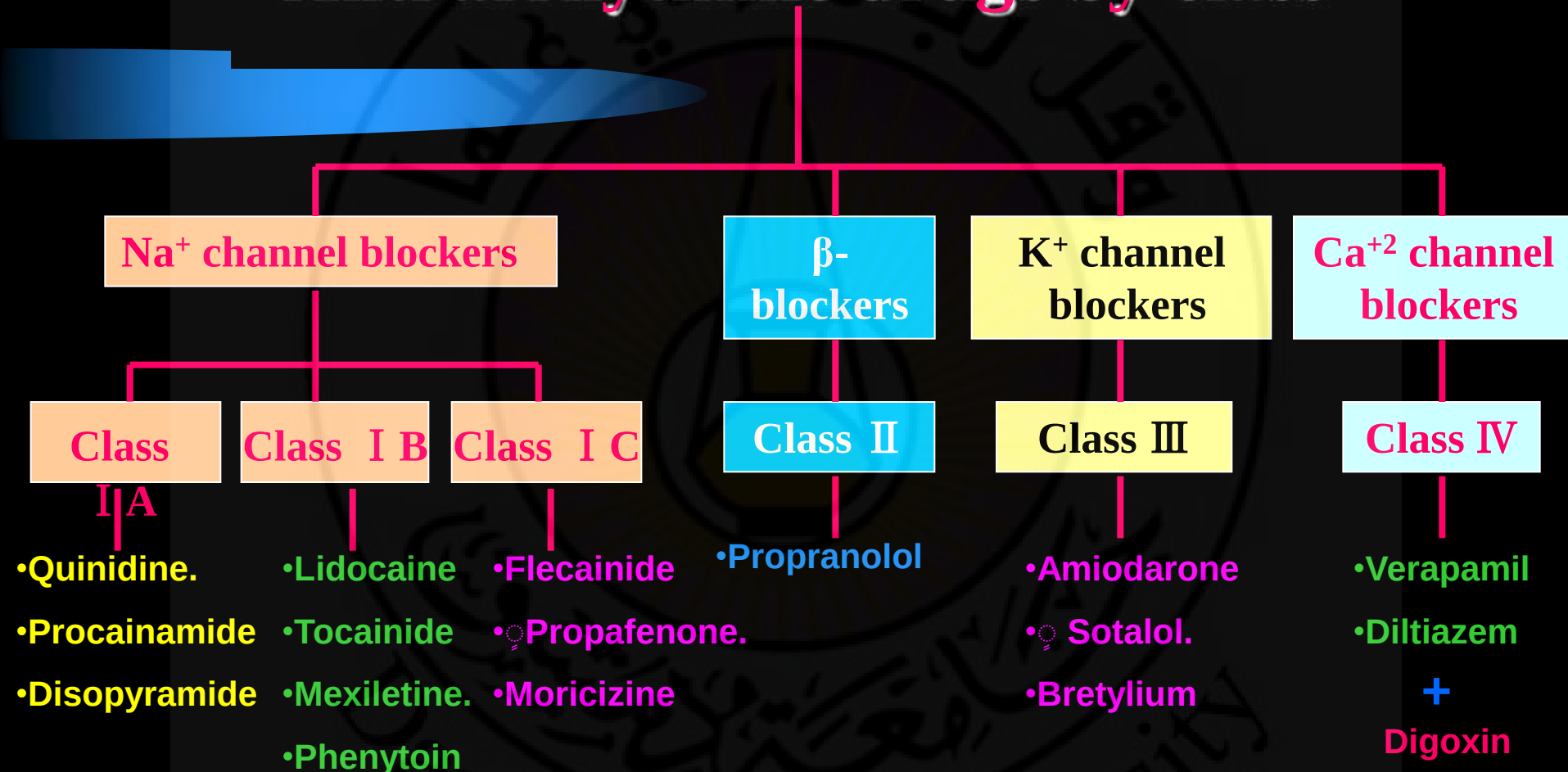
Adenosine

Side effects

- ✗ Dyspnea.
- ✗ Flushing.
- ✗ Chest pain.
- ✗ Arrhythmias.

➡ Theophylline and other methylxanthines antagonize Adenosine

Anti arrhythmic drugs by class



Anti arrhythmic drugs are divided into classes by a system loosely based on the channel or receptor involved: I, Sodium channel blockers; II, β- blockers; III, potassium channel blockers, and IV, Calcium channel blockers

Digoxin

Pharmacokinetics

 **A:** PO / IV. 36 hour half- life.

 **E:** Excreted unchanged in urine,
25% protein bound.

□ Digoxin □

- Only drug which increases automaticity of ectopic pacemakers.
- Slows conduction velocity through- out.
- Complex actions on refractory period.
- Increases parasympathetic tone.



□ Digoxin □

□ Clinical Uses □

▣ *Atrial fibrillation, atrial flutter, Paroxysmal atrial tachycardia.*



Side effects

Digoxin

-  *Digitalis intoxication.*
-  *Arrhythmias.*
-  *vomiting.*
-  *Headache.*
-  *Visual disturbances.*
-  *Complete heart block and accelerated junctional rhythm.*



Coronary Heart Disease (CHD)

Antianginal Drugs

Management of Myocardial Infarction

Antihyperlipidemic Drugs

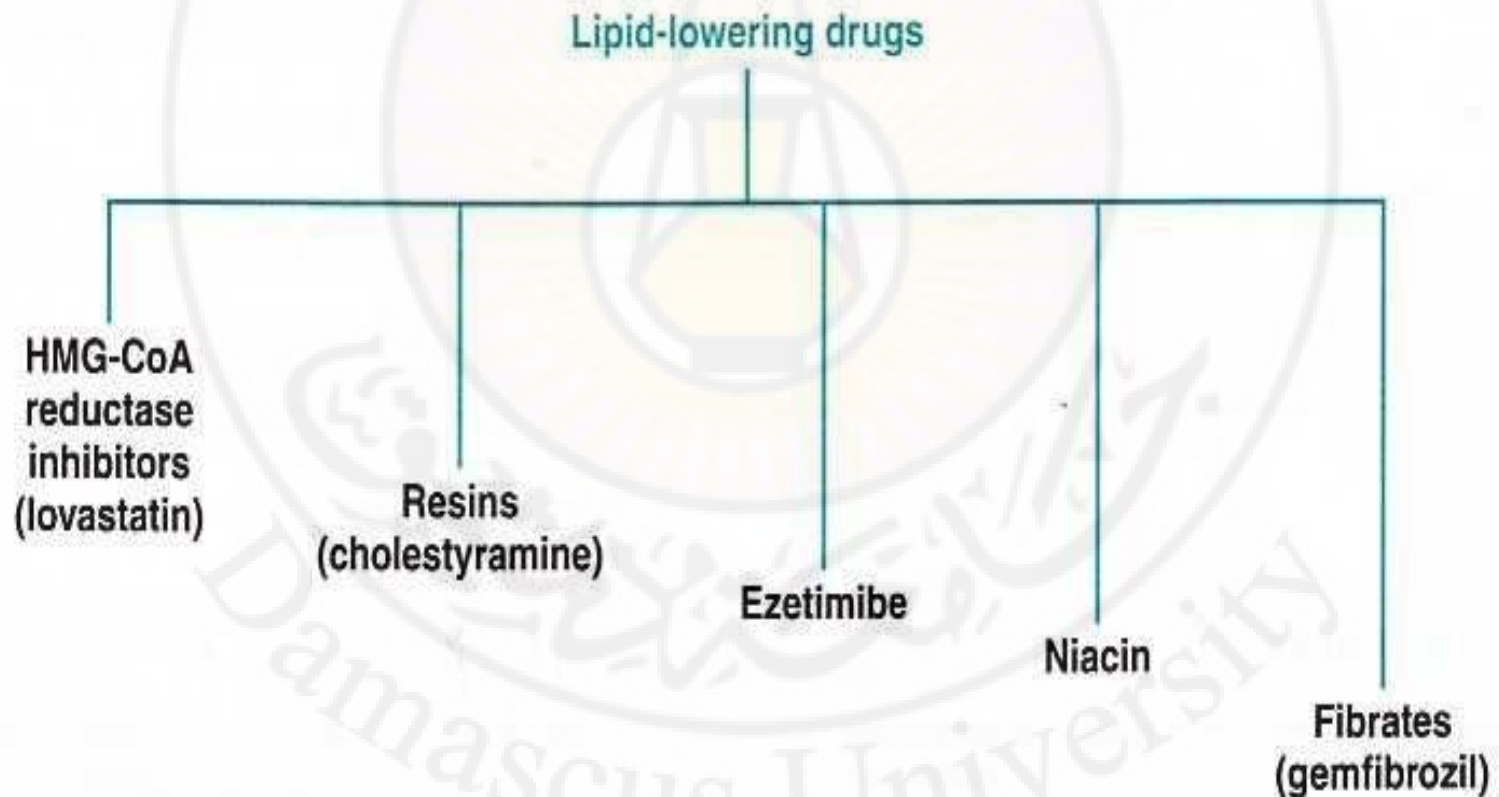
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Drugs affecting

Coagulation

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Atherosclerosis is the leading cause of death in the Western world. Drugs discussed in this chapter prevent the sequelae of atherosclerosis (heart attacks, angina, peripheral arterial disease, and stroke) and decrease mortality in patients with a history of cardiovascular disease and hyperlipidemia. Although the drugs are generally safe and effective, they can cause problems, including drug–drug interactions and rare toxic reactions in skeletal muscle and the liver.



Antihyperlipidemic Drugs by class

Bile acid
sequestrants



•Cholestyramine.
Cholestipol

Nicotinic acid



Niacin

HMG- CoA
reductase
inhibitors



Lovastatin.
Simvastatin.
•Pravastatin.
Fluvastatin.
Atorvastatin.
Cervastatin.

Fibric acid
derivatives



•Gemfibrozil.
Clofibrate
Fenofibrate

Antihyperlipidemic Drugs by class

Bile acid
sequestrants



- Cholestyramine.
- Cholestipol.

Nicotinic acid



Niacin

HMG- CoA
reductase
inhibitors



Lovastatin.
Simvastatin.
•Pravastatin.

Fluvastatin.
Atorvastatin.
Cervastatin.

Fibric acid
derivatives



•Gemfibrozil.
Clofibrate
Fenofibrate

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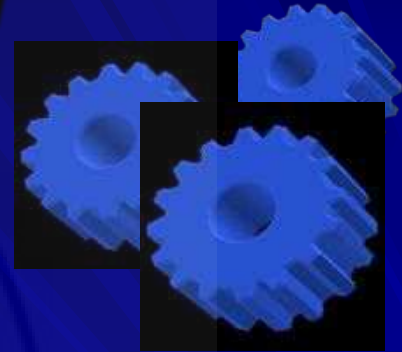
Pharmacokinetics

Cholestyramine & Cholestipol

- **A:** PO.
- **E:** Drug/ bile acid complex is excreted in feces.

Mechanism of action

Cholestyramine & Cholestipol



- ❖ ***Anion exchange resin that binds bile acids in the intestine and prevents reabsorption.***
- ❖ ***Reduction in bile acid reabsorption results in an increase in production of bile acids from cholesterol in the liver.***
- ❖ ***This increased demand for cholesterol by the liver increases the expression of LDL receptors by the liver.***
- ❖ ***LDL is cleared from the plasma more quickly due to the increased population of receptors.***

Clinical Uses

Cholestyramine & Cholestipol

- Greatest effect is seen at lowest doses of the drug.
- Decreases LDL 10- 30%.
- Increases HDL 2- 4%.
- Increases VLDL- TG levels 5- 30%.
- No effect on Lp(a).

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Side effects

- ❖ Abdominal pain.
- ❖ Bloating.
- ❖ Constipation.
- ❖ Pancreatitis.
- ❖ Interference with absorption of fat soluble vitamins (A, E, D, K)
- ❖ Binds to HMG- CoA reductase inhibitors.

Antihyperlipidemic Drugs by class

Bile acid
sequestrants

•Cholestyramine.
Cholestipol

Nicotinic acid

Niacin

HMG- CoA
reductase
inhibitors

Lovastatin.
Simvastatin.
•Pravastatin.
Fluvastatin.
Atorvastatin.
Cervastatin.

Fibric acid
derivatives

•Gemfibrozil.
Clofibrate
Fenofibrate

Pharmacokinetics

❖ Niacin

 **A** PO; rapidly absorbed.

 **M** Extensive first-pass hepatic metabolism.

 **E** Metabolites and parent drug excreted in urine.

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Mechanism of action

❖ Niacin

- ❖ Decreases the production of VLDL.
- ❖ Increases circulating levels of HDL.
- ❖ Decreases Lp(a).

Side effects

Niacin

- ❖ Acanthosis nigricans.
- ❖ Aggravation of asthma.
- ❖ Atrial arrhythmias.
- ❖ Cutaneous flushing.
- ❖ Gastritis/ ulcer disease.
- ❖ Glucose intolerance.
- ❖ Hepatitis.
- ❖ Hyperuricemia.
- ❖ increased risk of hepatotoxicity at dose required for sustained release formula: adjust dose when switching from sustained release form to normal oral form.

Clinical Uses

Niacin

- ▣ Decreases LDL 10- 25%.
- ▣ Decreases VLDL- TG 50%.
- ▣ Increases HDL 30- 40%.

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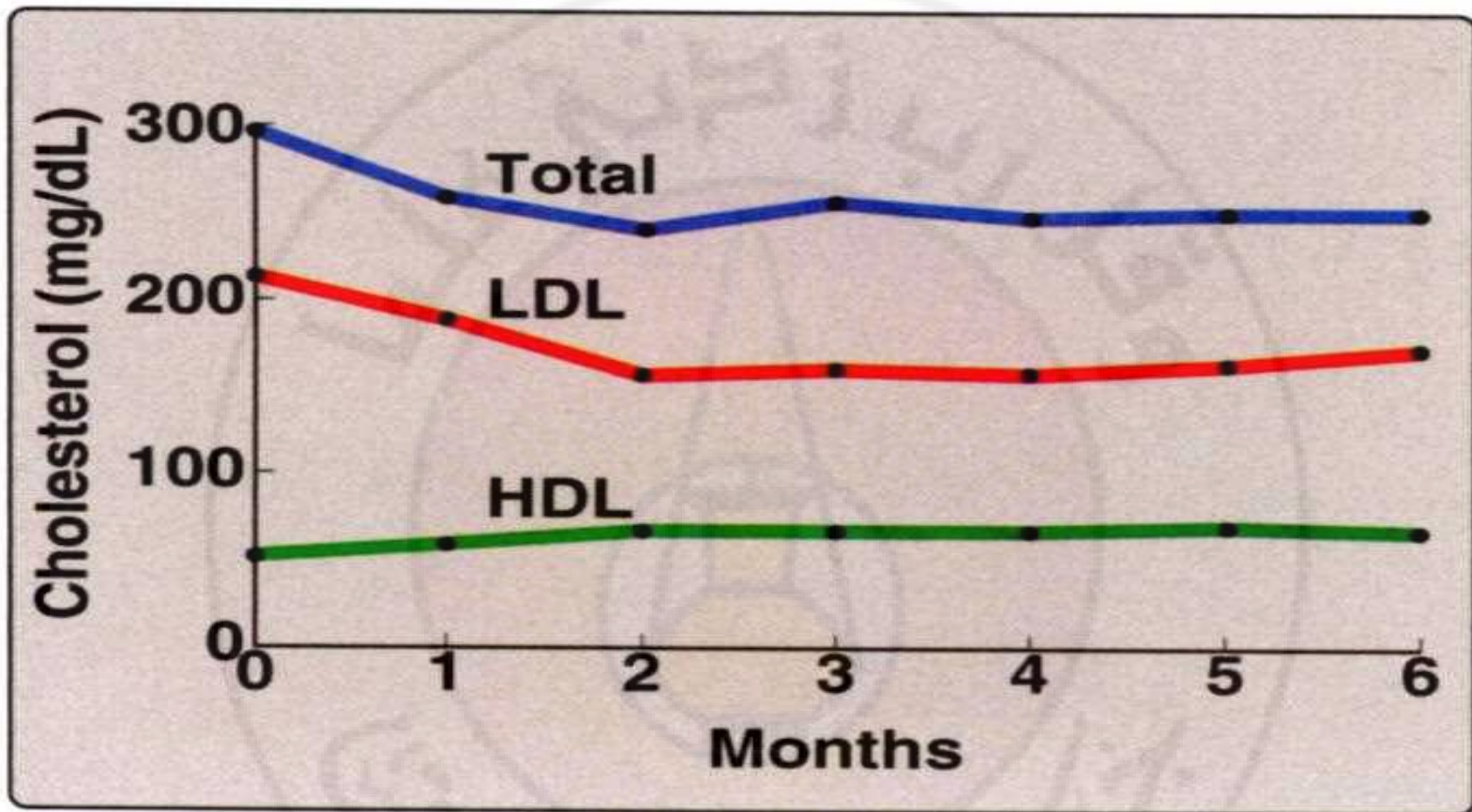


Figure 21.10

Plasma levels of cholesterol in hyperlipidemic patients during treatment with *niacin*.

Antihyperlipidemic Drugs by class

Bile acid
sequestrants

•Cholestyramine.
Cholestipol

Nicotinic acid

Niacin

HMG- CoA
reductase
inhibitors

•Lovastatin.
Simvastatin.
•Pravastatin.
Fluvastatin.
•Atorvastatin.
Cervastatin.

Fibric acid
derivatives

•Gemfibrozil.
Clofibrate
Fenofibrate

Pharmacokinetics

❖ **Statins**

- ❏ **A** PO; well absorbed.
- ❏ **M** Extensive first pass hepatic metabolism.
- ❏ **E**: Parent drug and metabolites excreted in urine.

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Mechanism of action

Statins

- Inhibit HMG- CoA reductase, the enzyme required for cholesterol synthesis.
- Increased production of LDL receptors in the liver.
- Increased uptake of LDL from the plasma.
- Decrease VLDL secretion.

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Clinical Uses

Statins

- ▣ Decrease LDL 20- 50%.
- ▣ Decrease TG 10- 20%.
- ▣ Increase HDL 5- 10%.
- ▣ No effect on Lp(a).

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Side effects

Statins

- ❖ Elevated liver transaminases (3 times normal).
- ❖ Headaches.
- ❖ Myopathy (uncommon and dose dependent).
- ❖ Cataracts (unproven).

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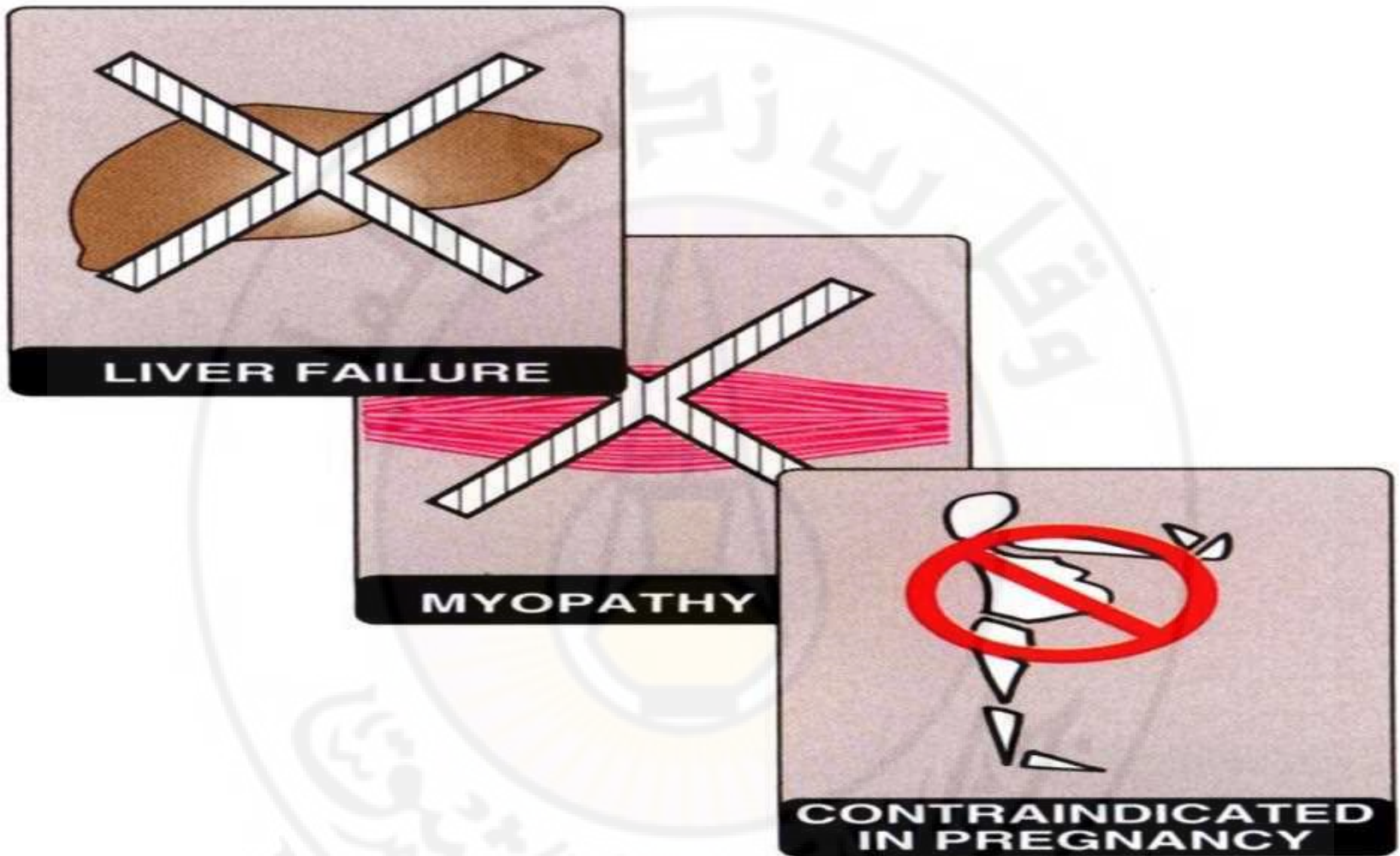


Figure 21.8

Some adverse effects and precautions associated with 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors.

Characteristic	<i>Atorvastatin</i>	<i>Fluvastatin</i>	<i>Lovastatin</i>	<i>Pravastatin</i>	<i>Rosuvastatin</i>	<i>Simvastatin</i>
Serum LDL cholesterol reduction produced (%)	50	24	34	34	50	41
Serum triacylglycerol reduction produced (%)	29	10	16	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	12	8	12
Plasma half-life (hr)	14	1-2	2	1-2	19	1-2
Penetration of central nervous system	No	No	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	20	10	13

Figure 21.7

Summary of 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors.

No drugs

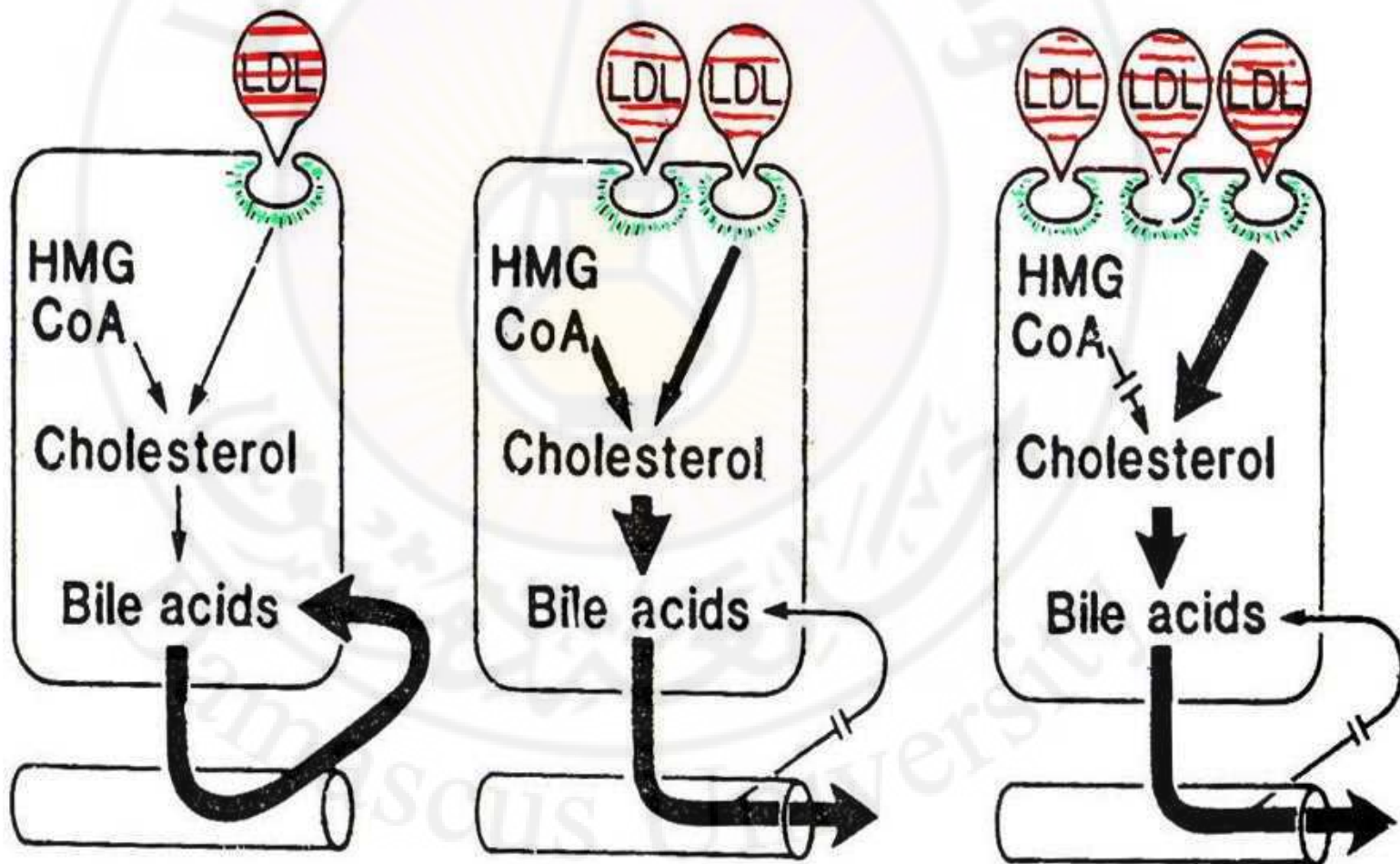
Bile acid
depletion

Reductase inhibitor
+
bile acid depletion

Plasma

Liver

Intestine



Pharmacokinetics

❖ Gemfibrozil

A: *PO; well absorbed.*

M: *Hepatic metabolism.*

E: *Parent drug and metabolites excreted in urine.*

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Pharmacokinetics

❖ Clofibrate

A: *PO; well absorbed.*

M: *Metabolized by serum enzymes then conjugated in liver.*

E: *Metabolites excreted in urine.*

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Pharmacokinetics

❖ Fenofibrate

A *PO*

M *Hepatic metabolism to active metabolite*

E *Metabolites excreted in*

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Mechanism of action

Gemfibrozil, Clofibrate & Fenofibrate

-  **Unknown but may increase the activity of LP lipase, thereby increasing the catabolism of VLDL.**
-  **May inhibit lipolysis of stored fat and decrease hepatic extraction of free fatty acids.**
-  **Stimulate the production of Apo A- 1, the major protein component of HDL.**

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Clinical Uses

Gemfibrozil, Clofibrate & Fenofibrate

- ▣ Decrease VLDL- TG 40- 55%.
- ▣ Decrease LDL < 10%.
- ▣ Increase HDL 20%.
- ▣ May decrease platelet reactivity and aggregability and concentration of fibrinogen.

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Side effects

Gemfibrozil, Clofibrate & Fenofibrate

- ❖ Alopecia.
- ❖ Decreased libido.
- ❖ Drowsiness.
- ❖ GI distress.
- ❖ Lithogenicity of bile.
- ❖ Myositis.

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Side effects

Gemfibrozil, Clofibrate & Fenofibrate

- ❖ Neutropenia.
- ❖ Ventricular arrhythmias (clofibrate).
- ❖ Weight gain.
- ❖ LTU can lead to increased gallbladder toxicity, increased appendectomies, hepatotoxicity (Fenofibrate), and potential risk for human carcinogenesis.

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Antihyperlipidemic Drugs by class

Bile acid sequestrants

- Cholestyramine.
- Cholestipol.

Nicotinic acid

- Niacin

HMG- CoA reductase inhibitors

- Lovastatin.
- Simvastatin.
- Pravastatin.
- Fluvastatin.
- Atorvastatin.
- Cervastatin

Fibric acid derivatives

- Gemfibrozil.
- Clofibrate
- Fenofibrate.

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EZETIMIBE

A. MECHANISM AND EFFECTS

Ezetimibe is a prodrug that is converted in the liver to the active glucuronide form. It prevents gastrointestinal uptake of cholesterol and phytosterols, plant sterols that normally enter gastrointestinal epithelial cell but then are immediately transported back into the intestinal lumen.

By preventing absorption of dietary cholesterol and cholesterol that is excreted in bile, ezetimibe reduces the cholesterol in the tightly regulated hepatic pool. A compensatory increase in the synthesis of high-affinity LDL receptors increases the removal of LDL lipoproteins from the blood.

As monotherapy, ezetimibe reduces LDL cholesterol by about 18% (see Table 35–2). When combined with a reductase inhibitor, it is even more effective.

B. CLINICAL USE

Ezetimibe is used for treatment of hypercholesterolemia (see Table 35–1) and phytosterolemia, a rare genetic disorder that results from impaired export of phytosterols.

C. TOXICITY

Ezetimibe is well tolerated. When combined with reductase inhibitors, it may increase the risk of hepatic toxicity. Serum concentrations of the glucuronide form are increased by fibrates and reduced by cholestyramine.

Table 35–2. Lipid-modifying effects of antihyperlipidemic drugs.

Drug	LDL Cholesterol	HDL Cholesterol	Triglyceride
Atorvastatin	–25% to –40%	+5% to –10%	↓↓
Fluvastatin	–20% to –30%	+5% to –10%	↓
Lovastatin ^a	–25% to –40%	+5% to –10%	↓
Resins	–15% to –25%	+5%	± or ↑ ^b
Ezetimibe	–13% to 19%	+3%	±
Fibrates	–10% to –15%	+15% to –20%	↓↓
Niacin	–15% to –40%	+25% to –35%	↓↓

^aPravastatin and simvastatin have effects similar to those of lovastatin.

^bResins can increase serum triglyceride concentrations in some patients with familial combined hypercholesterolemia.

±, variable, if any.

Modified, with permission, from Tierney LM, McPhee SJ, Papadakis MA, editors: *Current Medical Diagnosis & Treatment*, 3rd ed. McGraw-Hill, 2004.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG-CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Figure 21.14

Characteristics of hyperlipidemic drug families. HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LDL = low-density lipoprotein.

Table 35–1. The primary hyperlipoproteinemias and their drug treatment.^a

Condition	Single Drug	Drug Combination
Primary chylomicronemia (familial lipoprotein lipase or cofactor deficiency)	Dietary management	Niacin plus fibrate
Familial hypertriglyceridemia		
Severe	Niacin, fibrate	Niacin plus fibrate
Moderate	Niacin, fibrate	
Familial combined hyperlipidemia		
VLDL increased	Niacin, fibrate	
LDL increased	Niacin, reductase inhibitor, resin	Niacin plus resin or reductase inhibitor
VLDL, LDL increased	Niacin, reductase inhibitor	Niacin plus resin or reductase inhibitor
Familial dysbetalipoproteinemia	Fibrate, niacin	Fibrate plus niacin, or niacin plus reductase inhibitor
Familial hypercholesterolemia		
Heterozygous	Resin, reductase inhibitor, niacin, ezetimibe	Two or 3 of the individual drugs
Homozygous	Niacin, atorvastatin	Combinations of the individual drugs used for the heterozygous disorder

^aReproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.

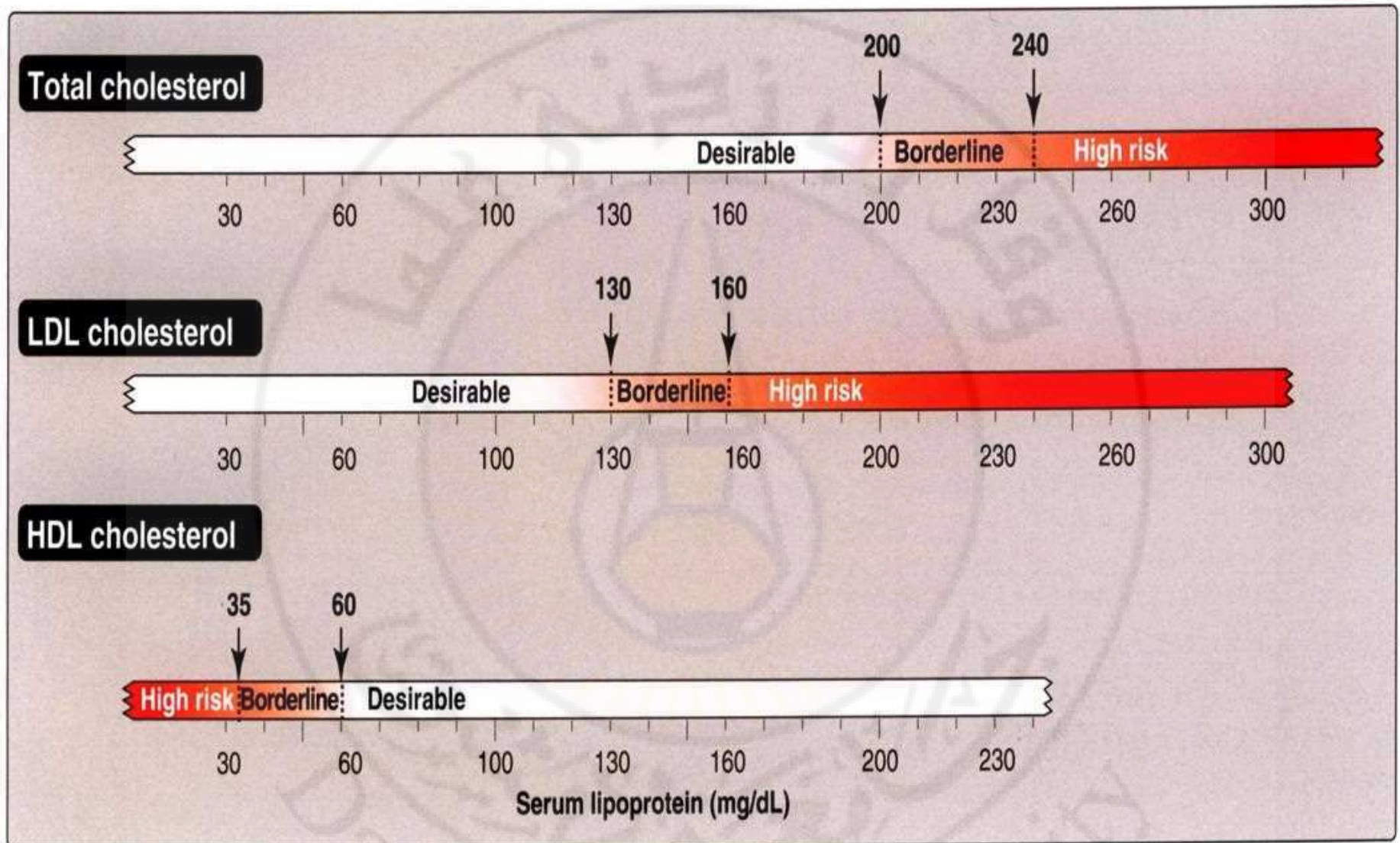


Figure 21.4

Goal lipoprotein levels achieved with dietary or drug therapy for the prevention of coronary heart disease. [Note: Lower goals for total and LDL cholesterol are recommended for patients with a history of heart disease.]

شكراً على الإصغاء

Damascus University

Cardiovascular system



Congestive Heart Failure

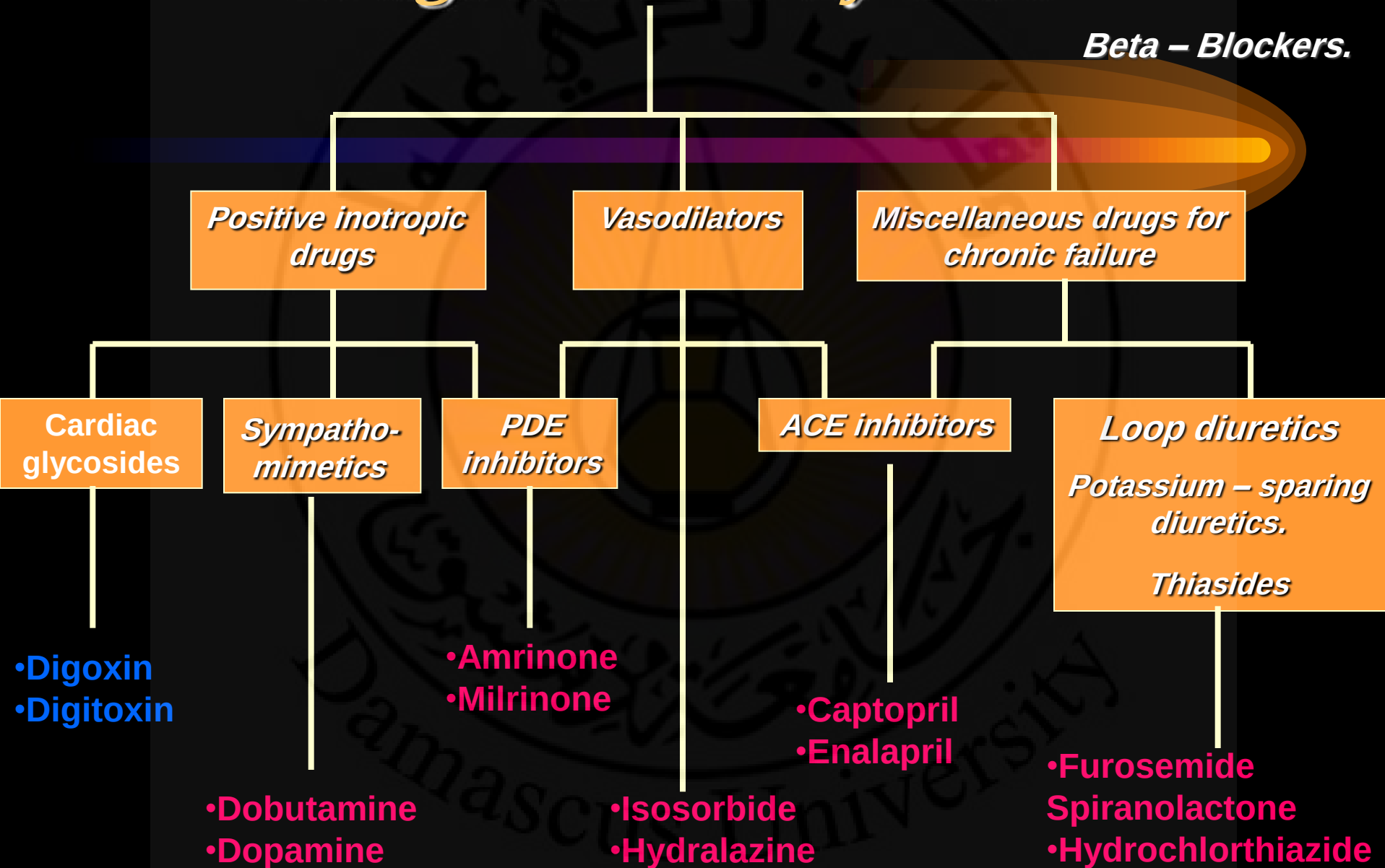
(CHF)



Exhaustion during physical activity may be a symptom of Heart Disease which could lead to Congestive Heart Failure.

Drugs for CHF by class

Beta – Blockers.



Pharmacokinetics

Digitoxin **(Digitaline)**

- **A:** PO
- **M:** metabolized in liver.
- **E:** Metabolites excreted unchanged in bile.

Digoxin **(Lanoxin, lanoxicaps)**

- **A:** IV or PO
- **M:** Small amount metabolized in liver
- **E:** Majority excreted unchanged in urine.

Mechanism of action



- **Inhibit the Na^+ / K^+ ATPase, leading to an increase in IC Na^+**
- **Increase in IC Na^+ leads to a decrease in the activity for the $\text{Na}^+ / \text{Ca}^{+2}$ exchanger, resulting in an increase in IC Ca^{+2} .**
- **Increase in IC Ca^{+2} means that the amount of Ca^{+2} present during an AP is higher, leading to a more forceful contraction.**
- **Direct electrical effects on the heart include decrease in AP duration, ectopic beats, and arrhythmias.**

Clinical Uses



- *Treatment of CHF.*
- *Therapeutic index is very low (high risk).*
- *Digitalis compounds must be administered slowly and in small doses*

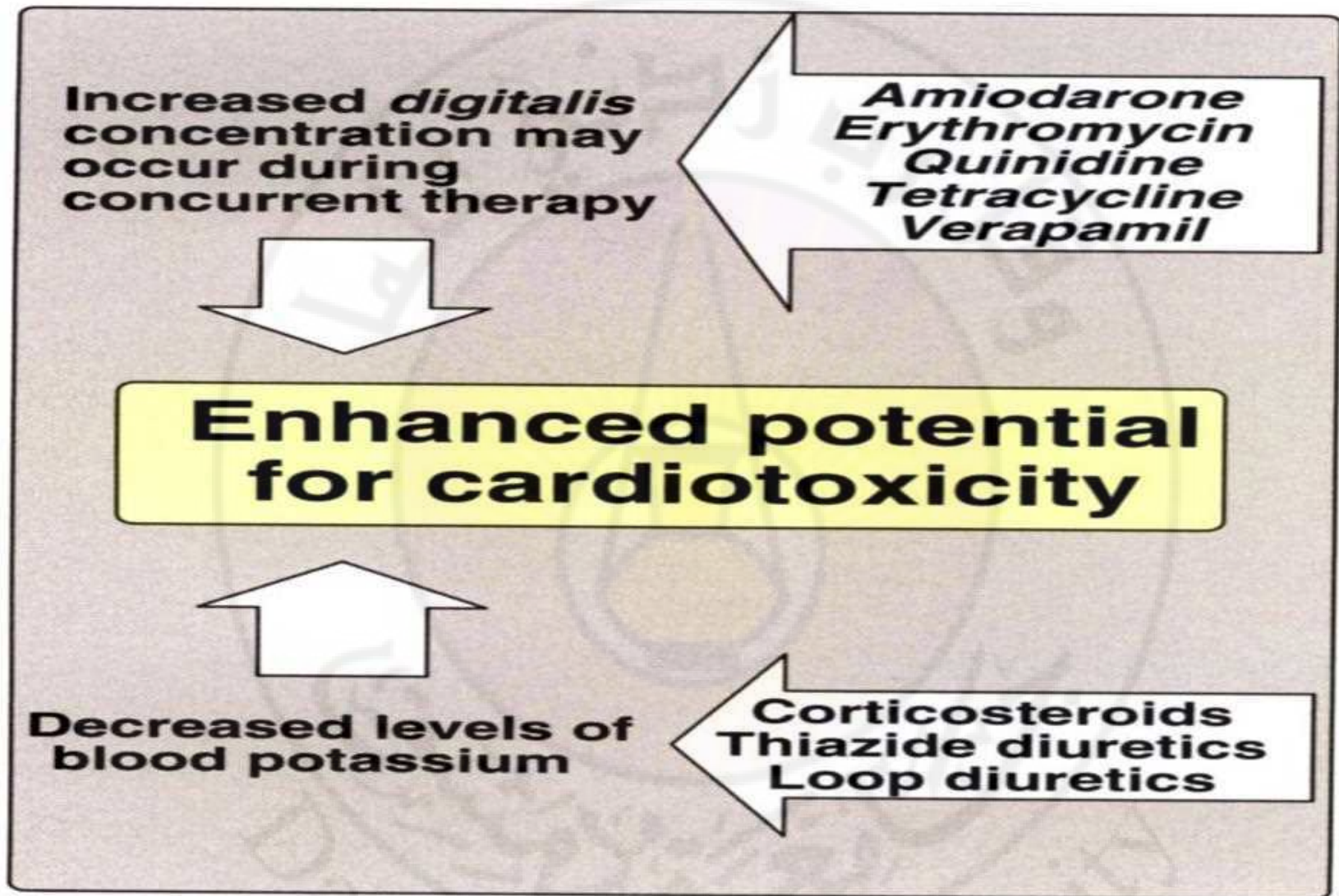
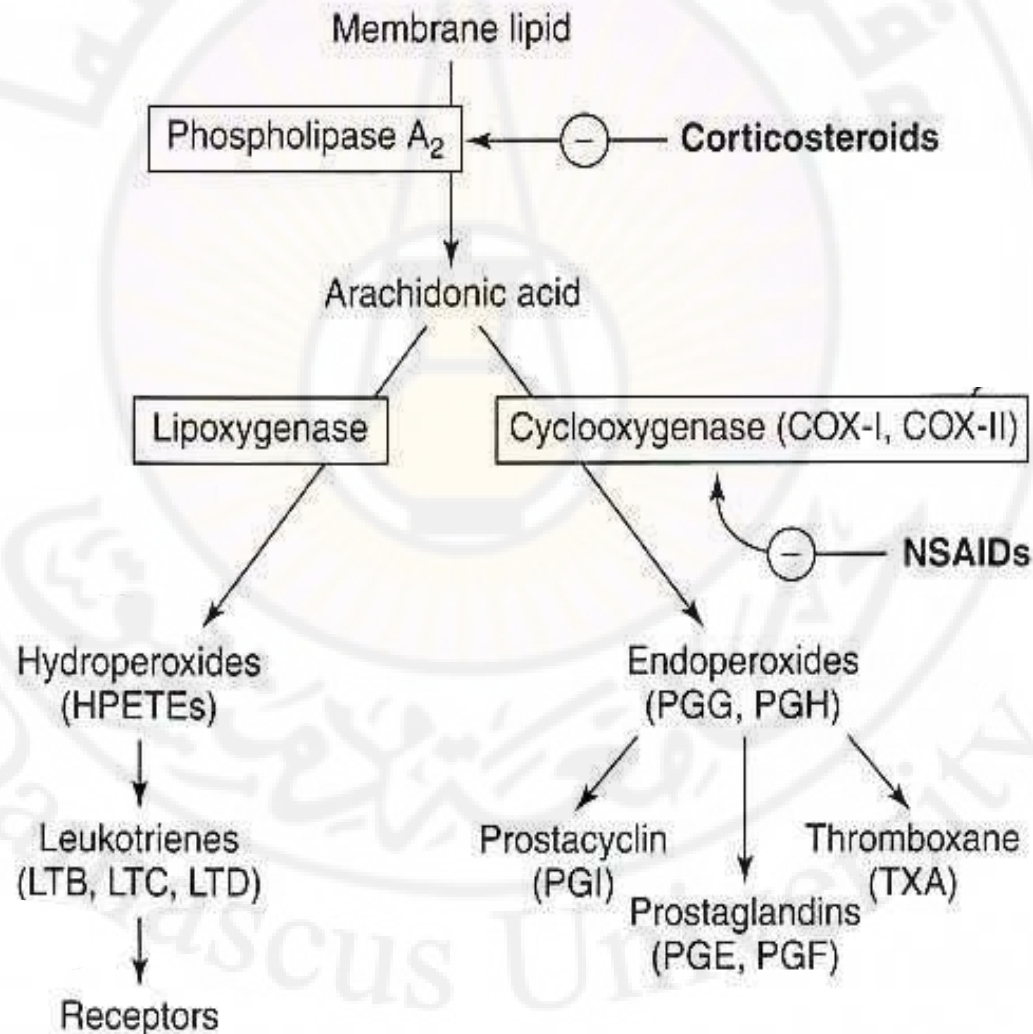


Figure 16.11

Drugs interacting with *digoxin* and other digitalis glycosides.

The eicosanoids are an important group of endogenous fatty acid derivatives that are produced from arachidonic acid. Arachidonic acid is derived from cell membrane lipids. Two major families of eicosanoids are produced by the enzymes cyclooxygenase and lipoxygenase.



Side effects

- ***Cardiac side effects include:***

1. AV junctional rhythm.
2. Premature ventricular depolarization.
3. AV blockade.

- ***Non-cardiac side effects include:***

1. Nausea.
2. Color vision abnormality.
3. Anorexia.
4. Diarrhea.
5. Disorientation.
6. Gynecomastia.
7. Digoxin levels in plasma double when co administered with quinidine.
8. Hypokalemia can increase the risk of toxicity by worsening arrhythmias.

Side effects

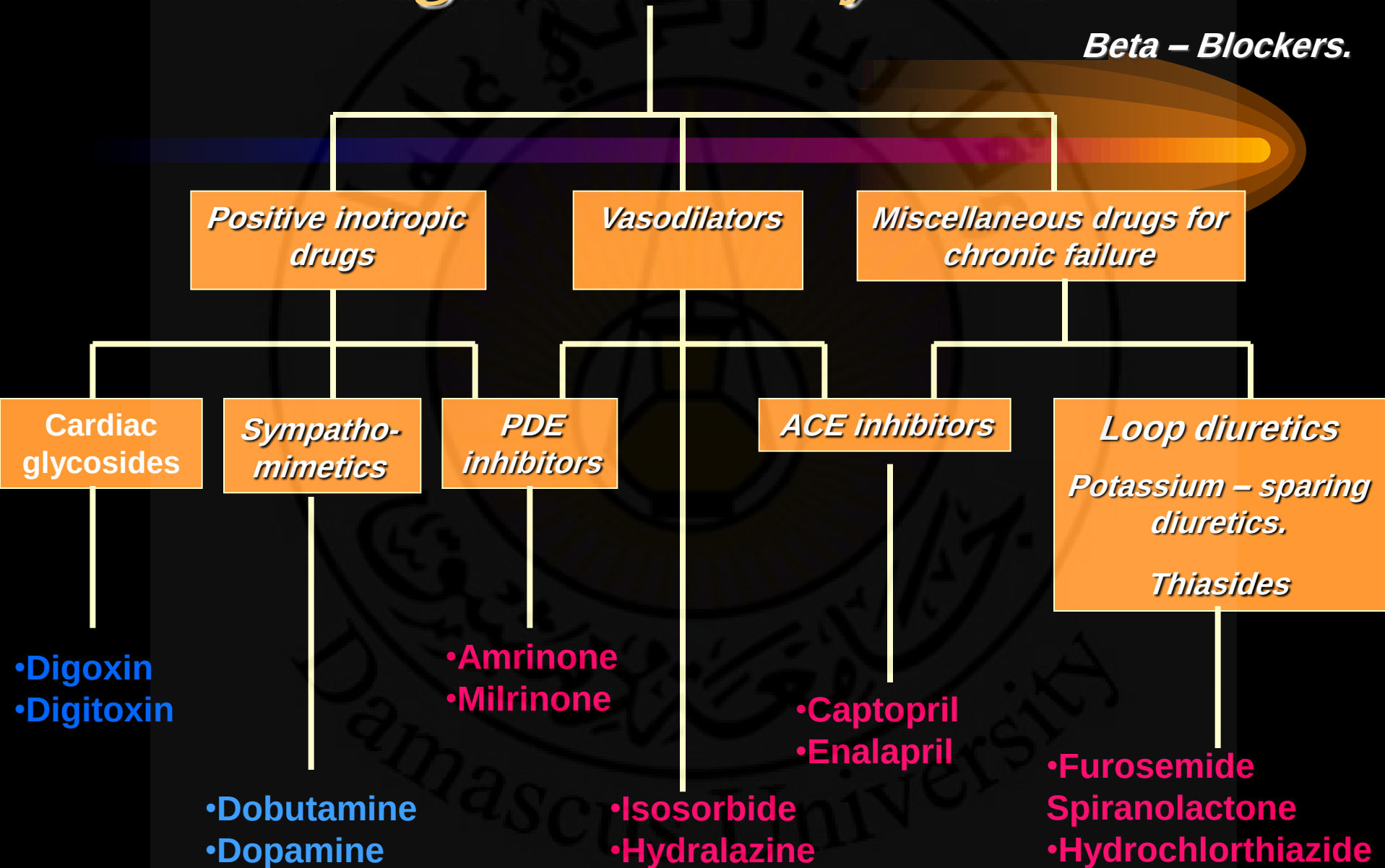
Cholestyramine &

Cholestipol

- ❖ Abdominal pain.
- ❖ Bloating.
- ❖ Constipation.
- ❖ Pancreatitis.
- ❖ Interference with absorption of fat soluble vitamins (A, E, D, K)
- ❖ Binds to HMG- CoA reductase inhibitors.

Drugs for CHF by class

Beta – Blockers.



Dobutamine **(Dobutrex)**

- **A:** IV.
- **M:** metabolized in urine and plasma by COMT.
- **E:** Metabolites excreted in urine .

Dopamine **(Intropin)**

- **A:** IV.
- **M:** Metabolized in liver, kidney, and plasma by MAO and COMT
- **E:** Metabolites excreted in urine .

Dopamine (Intropin)



Dobutamine (Dobutrex)

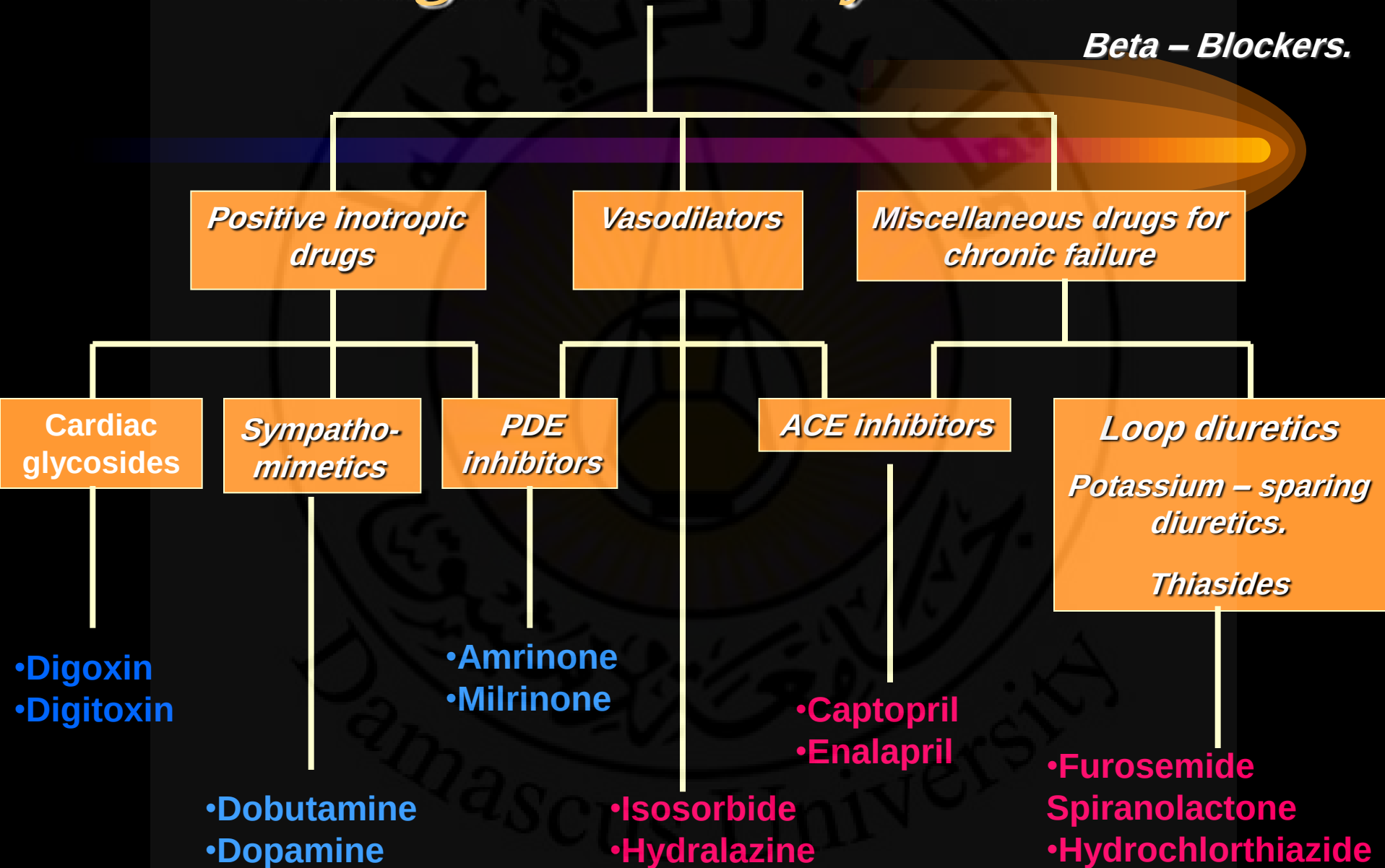
- Causes release of NE at the heart, which leads to β – adrenergic stimulation.
- Stimulates β_1 - receptors.
- Inhibits NE release in the periphery causing vasodilator.

- Leads to an elevation of cAMP and subsequent positive inotropic effects.
- Low chronotropic activity.

 ***Mechanism of action***

Drugs for CHF by class

Beta – Blockers.



Pharmacokinetics

Amrinone
(Inocor)

&

Milrinone
(Primacor)

- **A:** IV.
- **M:** Hepatic metabolism.
- **E:** Parent drug and metabolites excreted in urine and feces .

Clinical Uses

Amrinone
(Inocor)

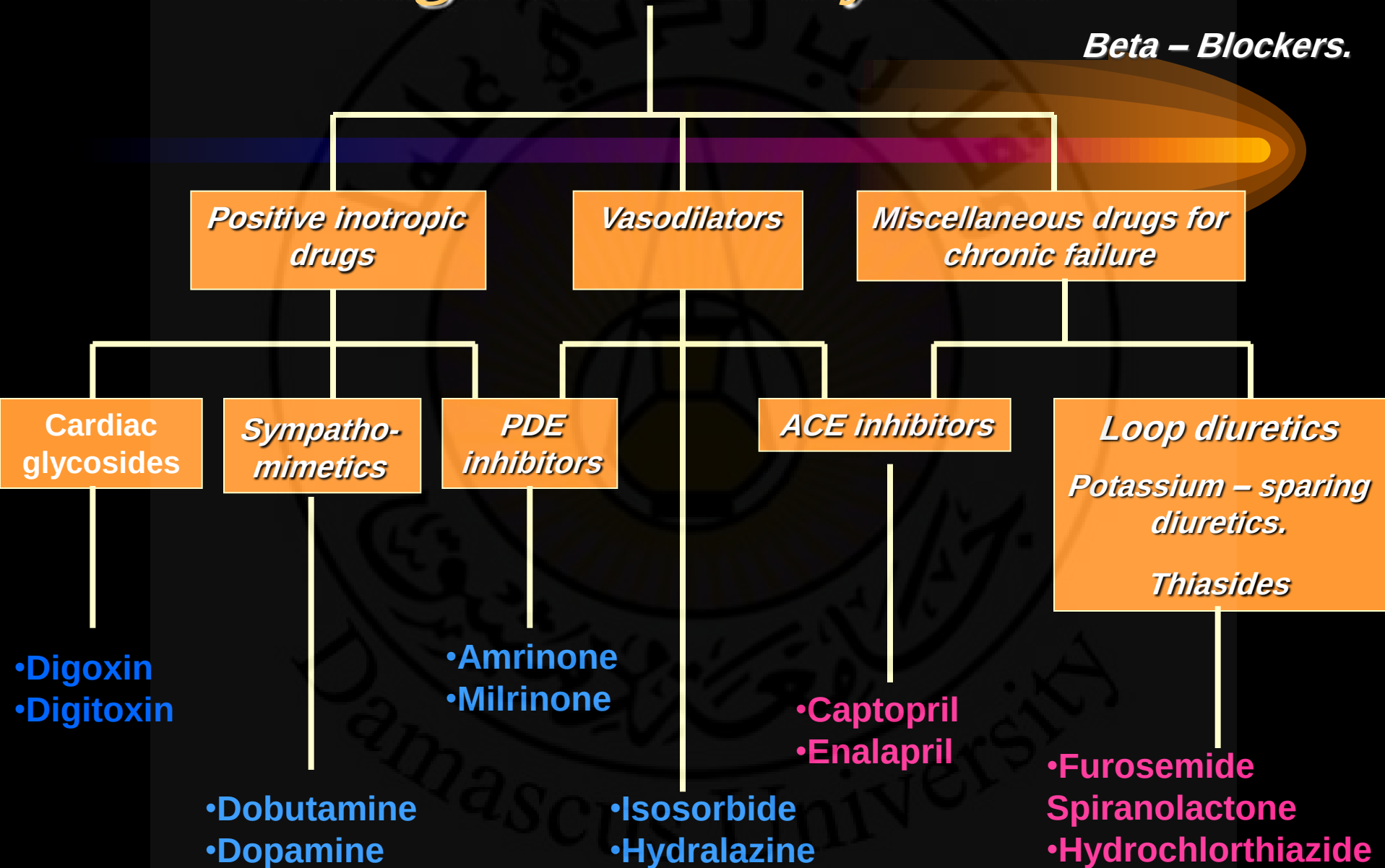
&

Milrinone
(Primacor)

- Treatment of acute CHF.

Drugs for CHF by class

Beta – Blockers.



Pharmacokinetics

Hydralazine (Apresoline)

- **A:** PO, IM, and IV.
- **M:** Extensive first-pass hepatic metabolism; hepatic acetylation (remember that certain patient population have varying rates of acetylation)
- **E:** Metabolites excreted in urine

Isosorbide dinitrate (Isodril, Sorbitrate)

- **A:** Sublingual, PO, IV, ointment, or patches.
- **M:** Hepatic metabolism to active metabolites.
- **E:** Metabolites excreted in urine .



Mechanism of action

❖ ***Reduce the workload of the heart by reducing the after load via arteriolar dilation and reducing the pre load via venous dilation.***

Mechanism of action

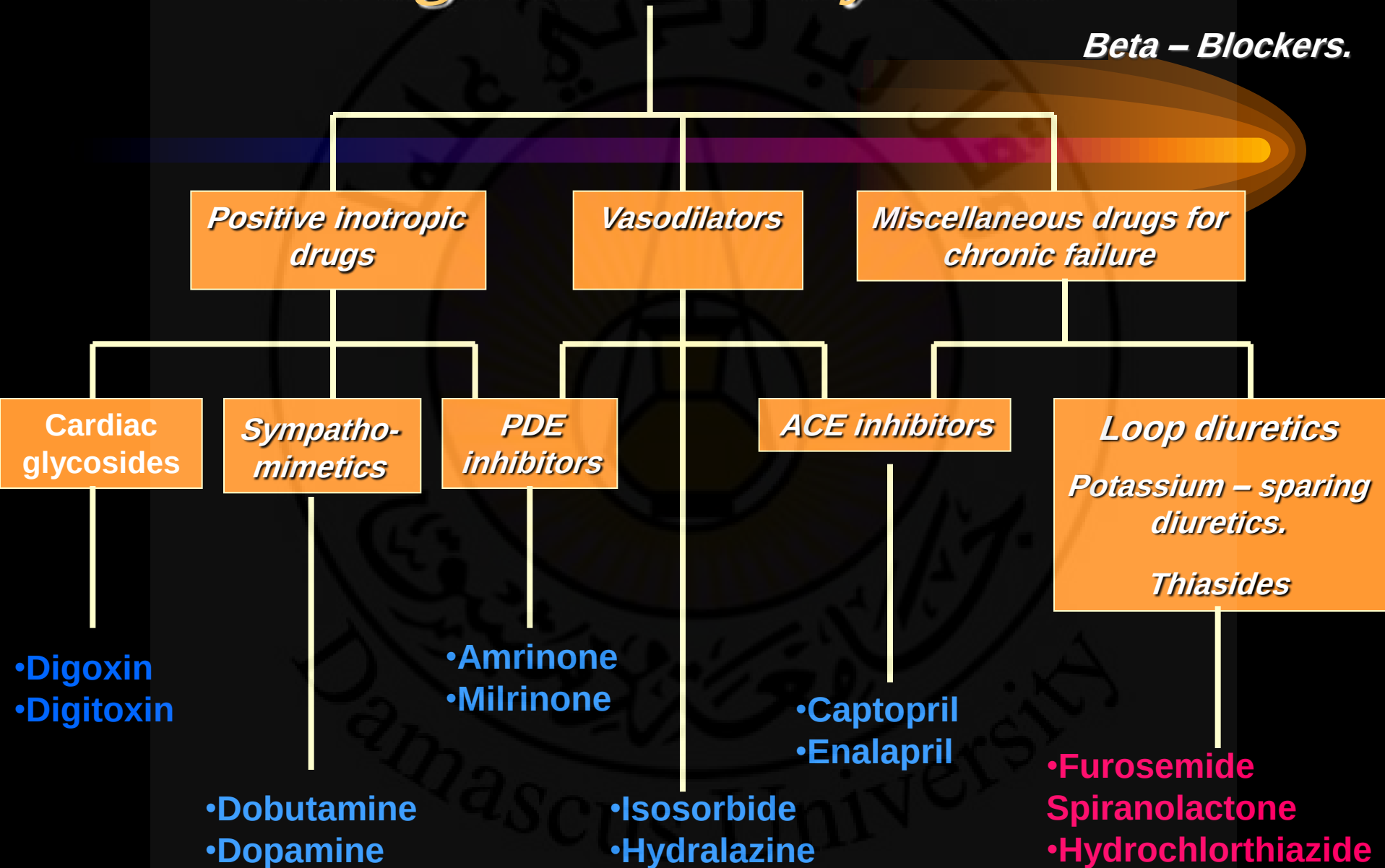
Hydralazine

- ◆ Arterial smooth muscle relaxation and vasodilation (probably through action on cAMP and Ca^{+2}).



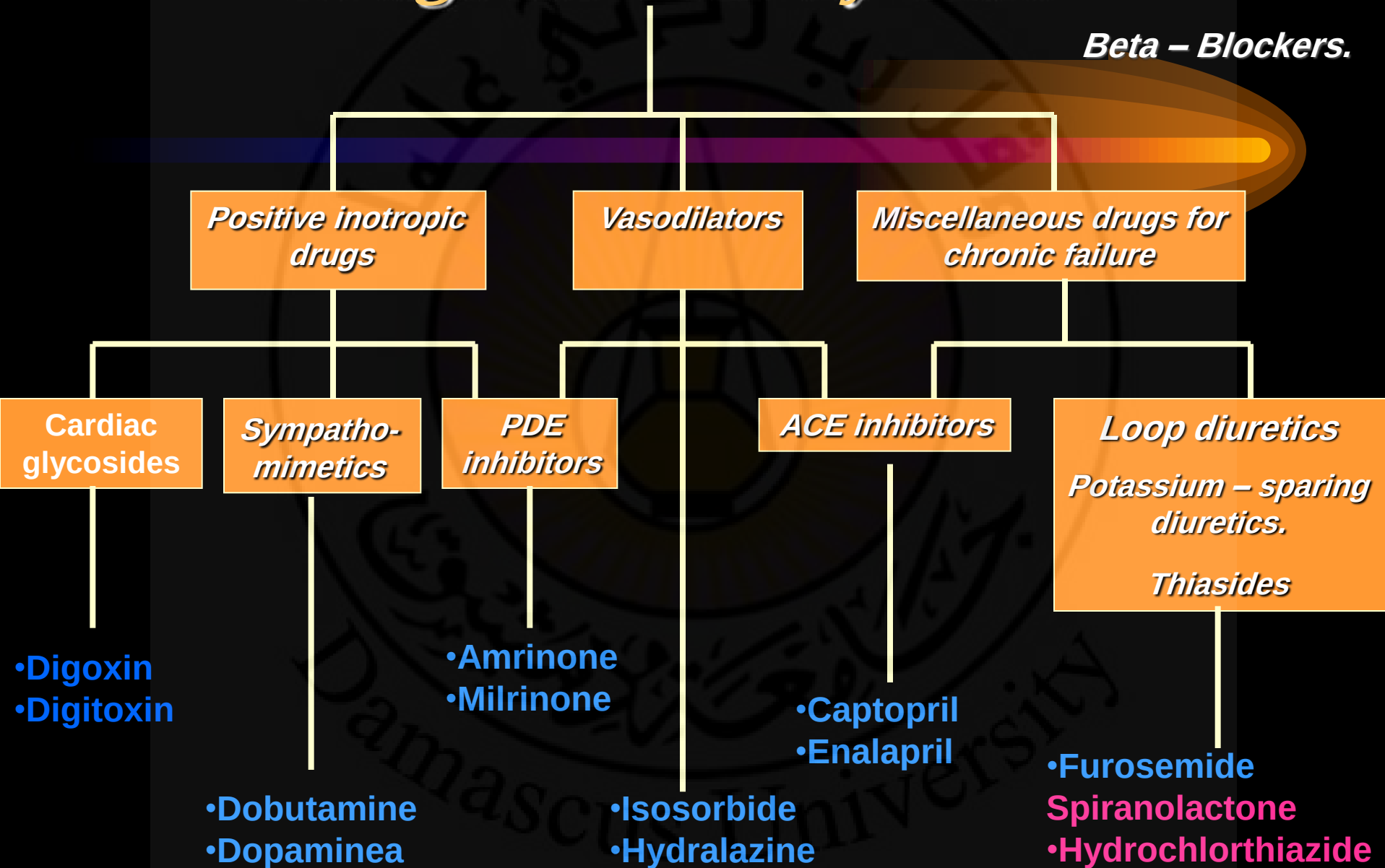
Drugs for CHF by class

Beta – Blockers.



Drugs for CHF by class

Beta – Blockers.





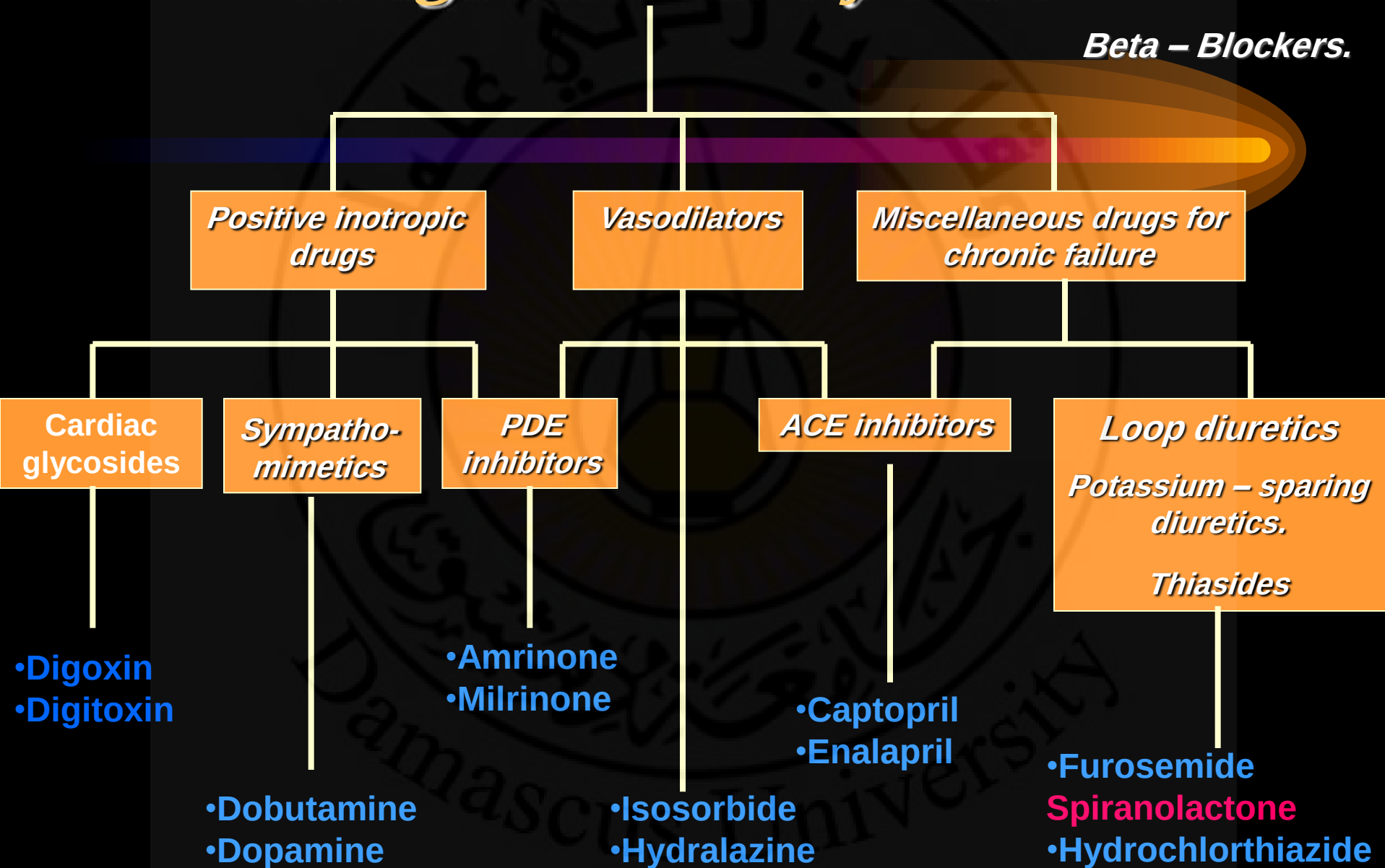
Pharmacokinetics

• ***Furosemide*** ***(Lasix)***

- ❖ ***A: IV, IM, and PO.***
- ❖ ***M: Metabolized to a small degree in the liver.***
- ❖ ***E: Metabolite and parent drug excreted in urine.***

Drugs for CHF by class

Beta – Blockers.



Pharmacokinetics

Spiranolactone ***(Aldactone)***

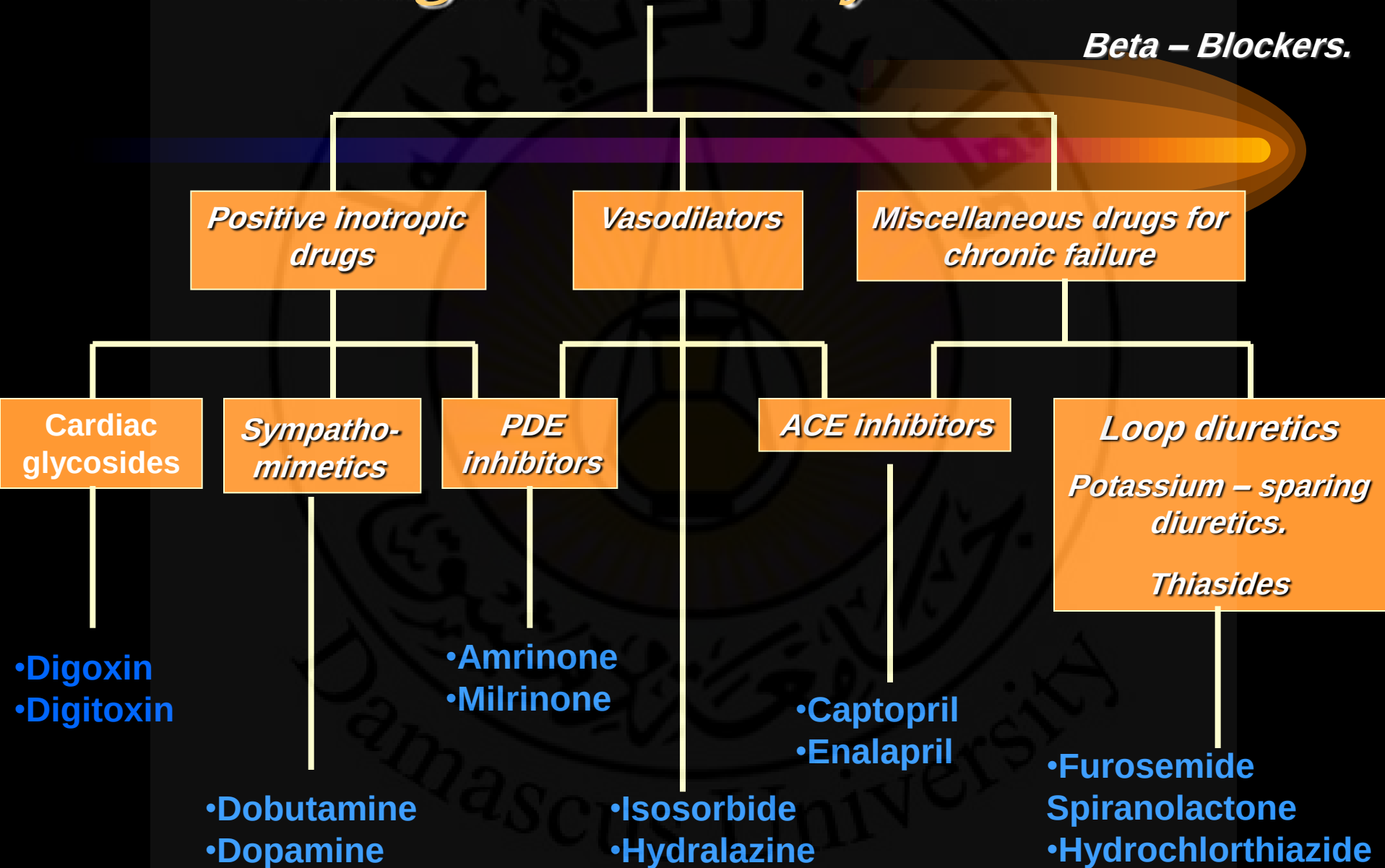
•**A:** ***PO.***

•**M:** ***Metabolized to active metabolites.***

•**E:** ***Majority of metabolites excreted in urine; remaining in feces.***

Drugs for CHF by class

Beta – Blockers.





Pharmacokinetics

• *Hydrochlorthiazide
(HCTZ, HydroDIURIL)*

❖ *A: PO.*

❖ *E: Unchanged in
urine.*

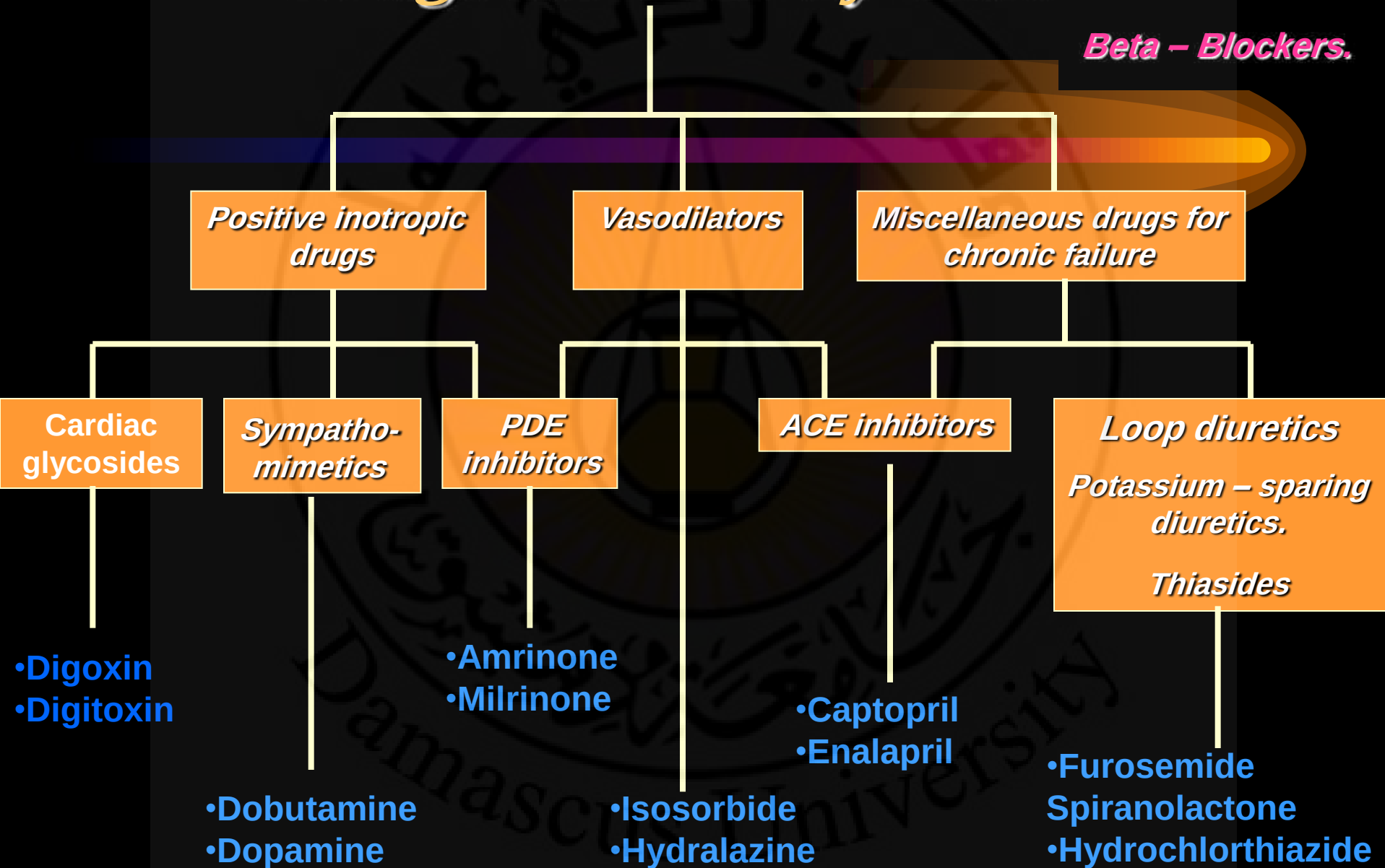
Clinical Uses



- *Long – term treatment of CHF.*
- *Also used in the treatment of hypertension.*

Drugs for CHF by class

Beta – Blockers.



Patients receiving triple therapy were least likely to experience worsening of heart failure compared to any of the other three treatment groups.

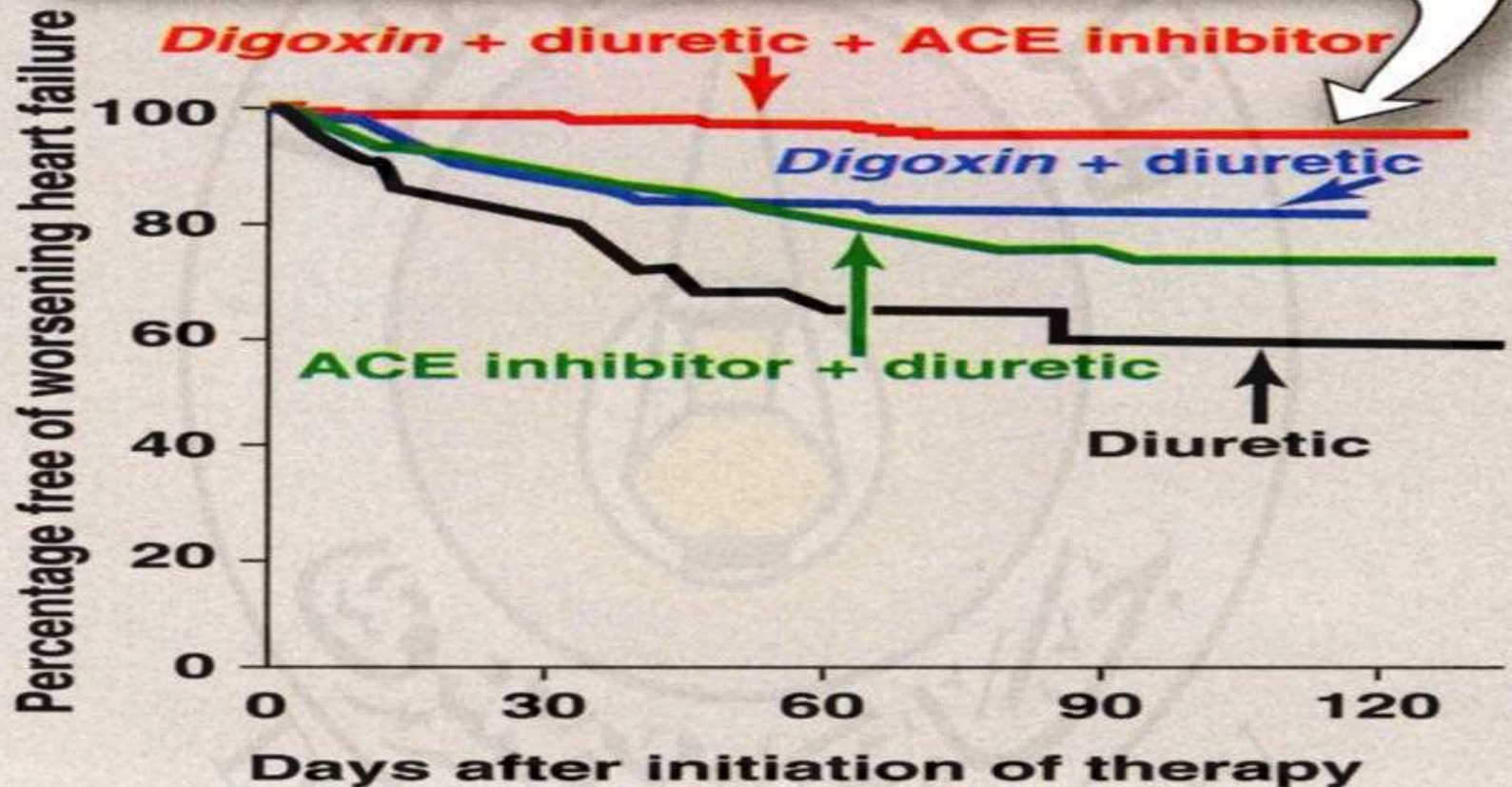


Figure 16.14

Use of multiple drugs in the treatment of heart failure. ACE = angiotensin-converting enzyme.

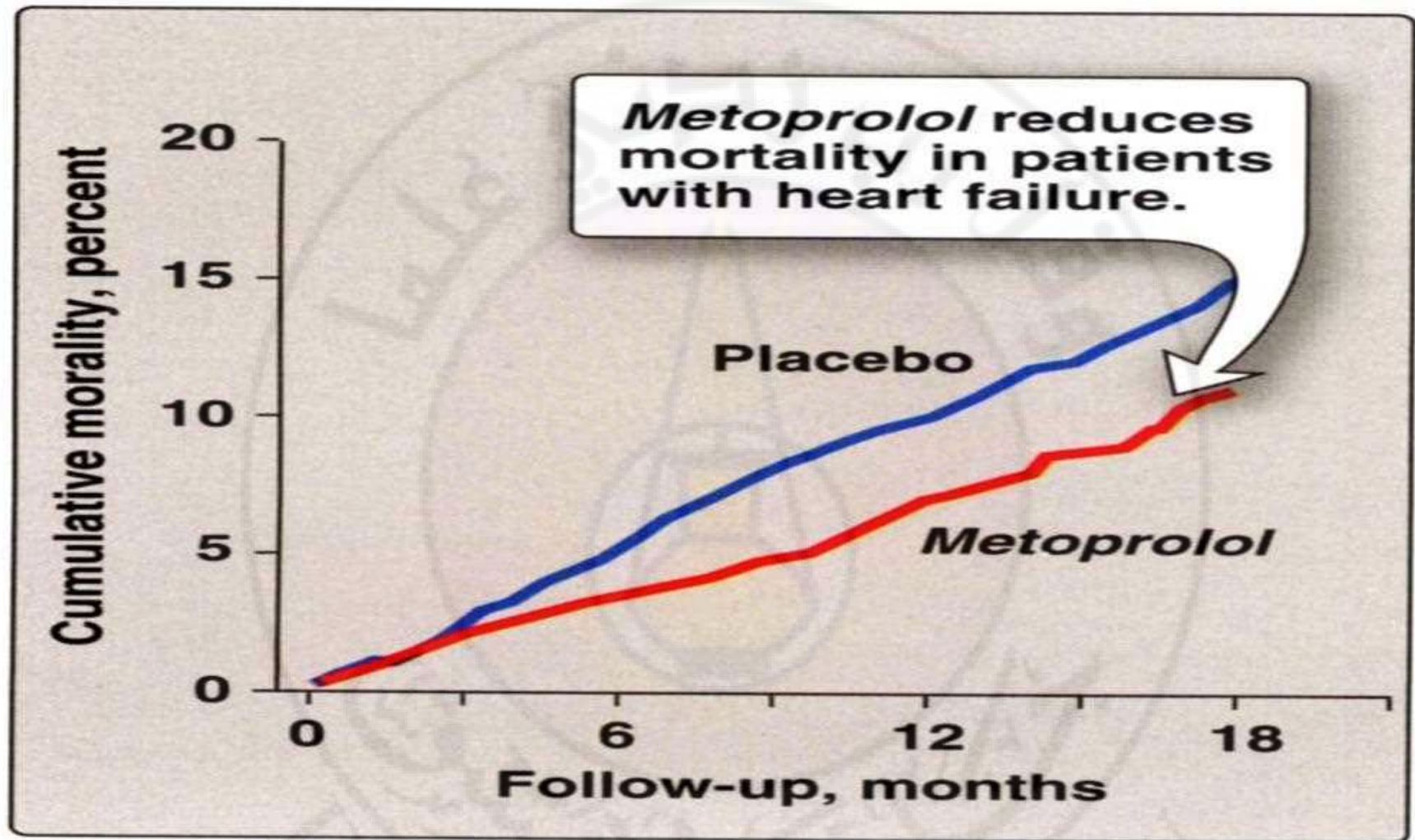


Figure 16.7

Cumulative mortality in patients with heart failure treated with placebo or *metoprolol*.

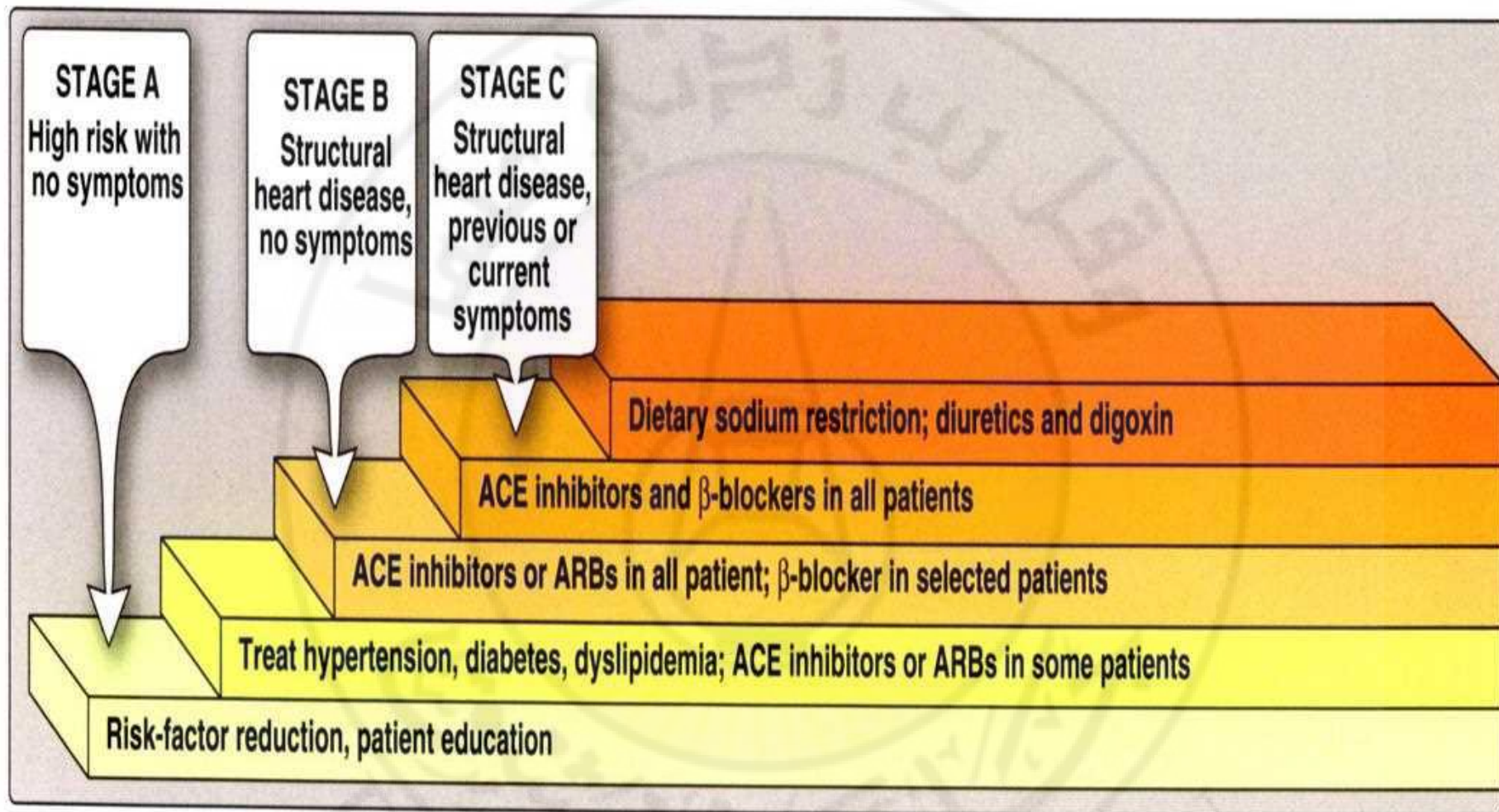


Figure 16.13

Treatment options for various stages of heart failure. ACE = Angiotensin-converting enzyme; ARB = angiotensin-receptor blockers. Stage D (refractory symptoms requiring special interventions) is not shown.

شكراً على الإصغاء

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شكراً على الإصغاء



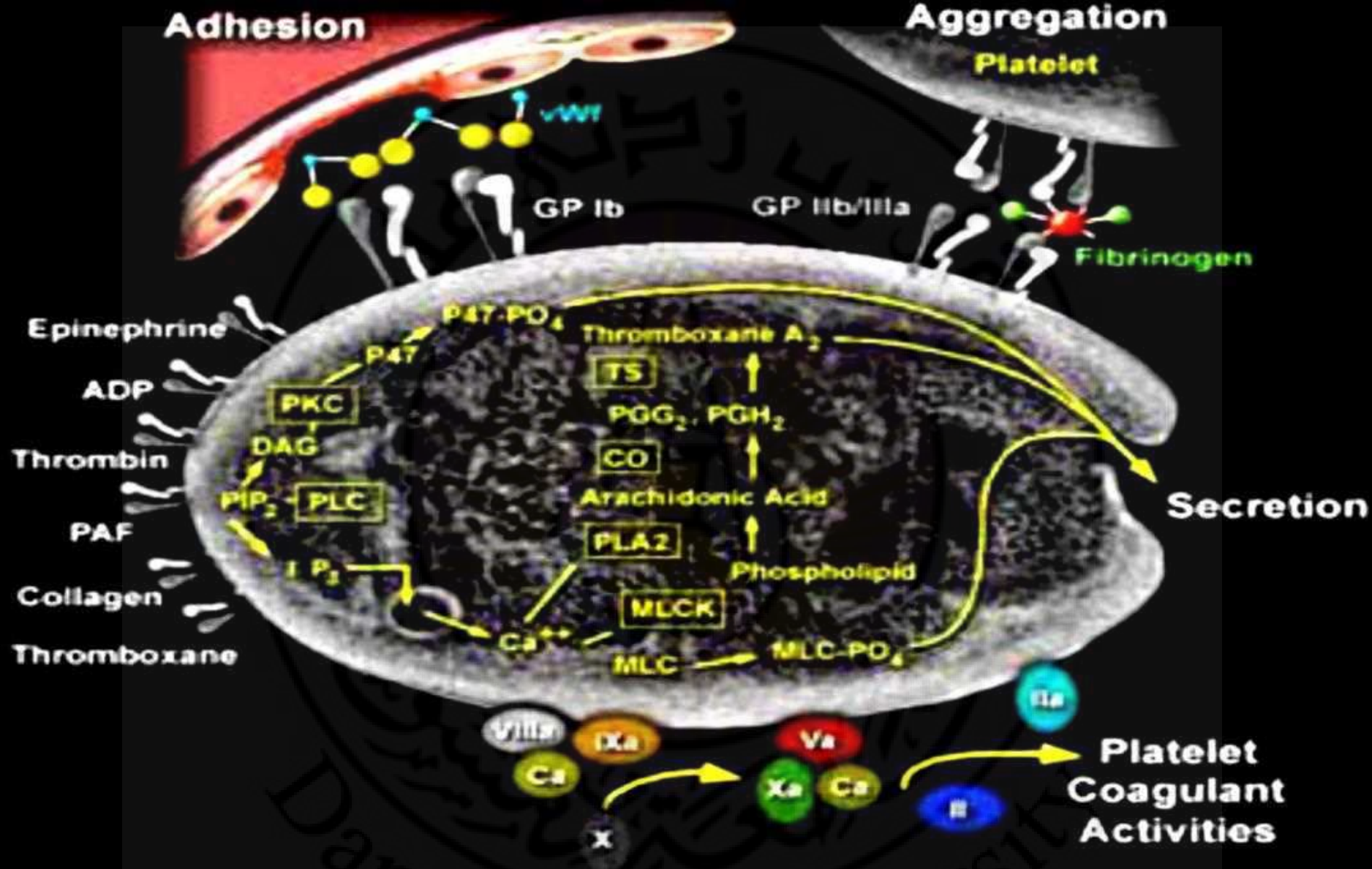
Coronary Heart Disease (CHD)

Antianginal Drugs

Management of Myocardial Infarction

Antihyperlipidemic Drugs

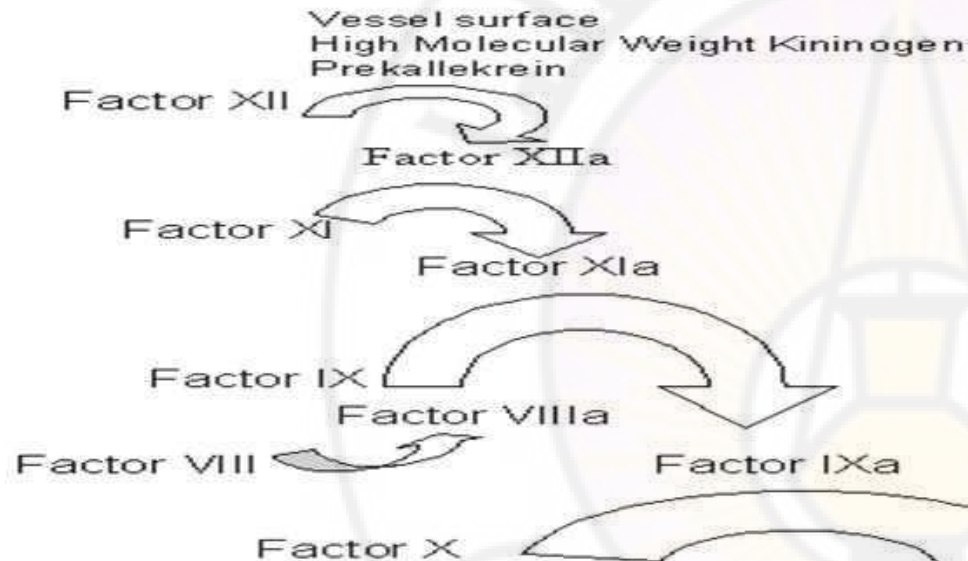
Drugs affecting Coagulation

Adhesion**Aggregation****Platelet****Fibrinogen****Secretion****Platelet
Coagulant
Activities**

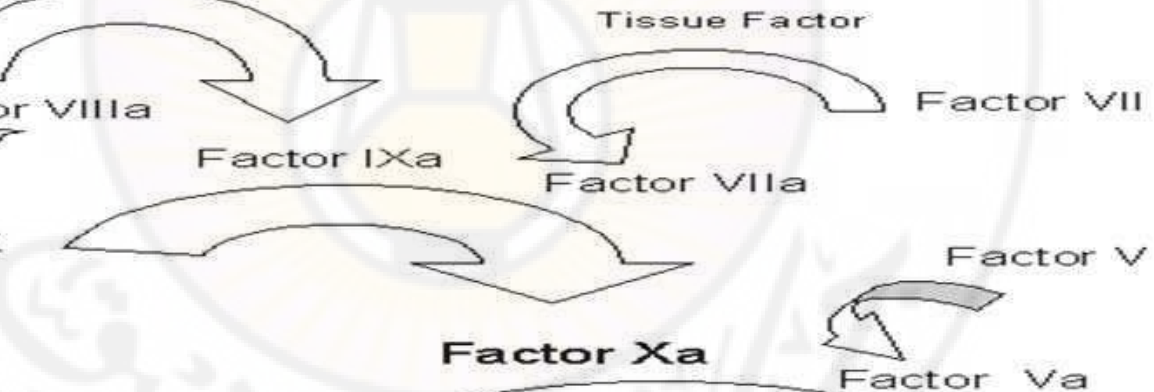
Source Adapted from Colman RW, et al. In Colman RW, et al, eds. *Hemostasis and Thrombosis. Basic Principles and Clinical Practice*. Philadelphia J.D. Lippincott Co., 1994:3.

The Classic Cascade

Intrinsic System



Extrinsic System

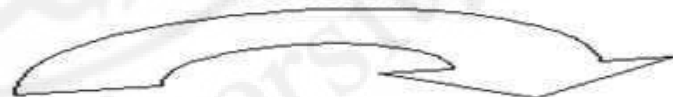


Prothrombin



Thrombin

Fibrinogen



Fibrin

Crosslinked Fibrin

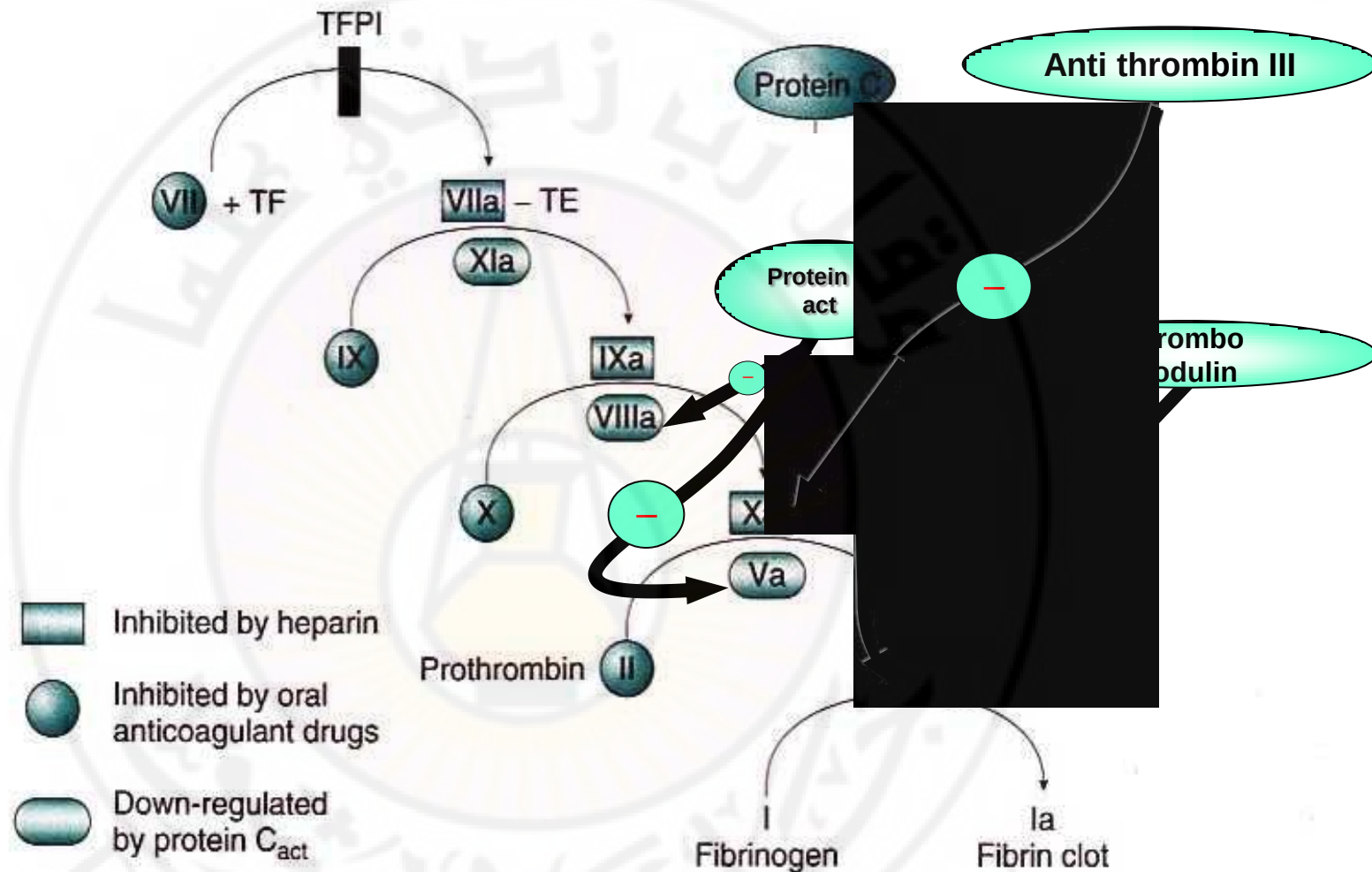
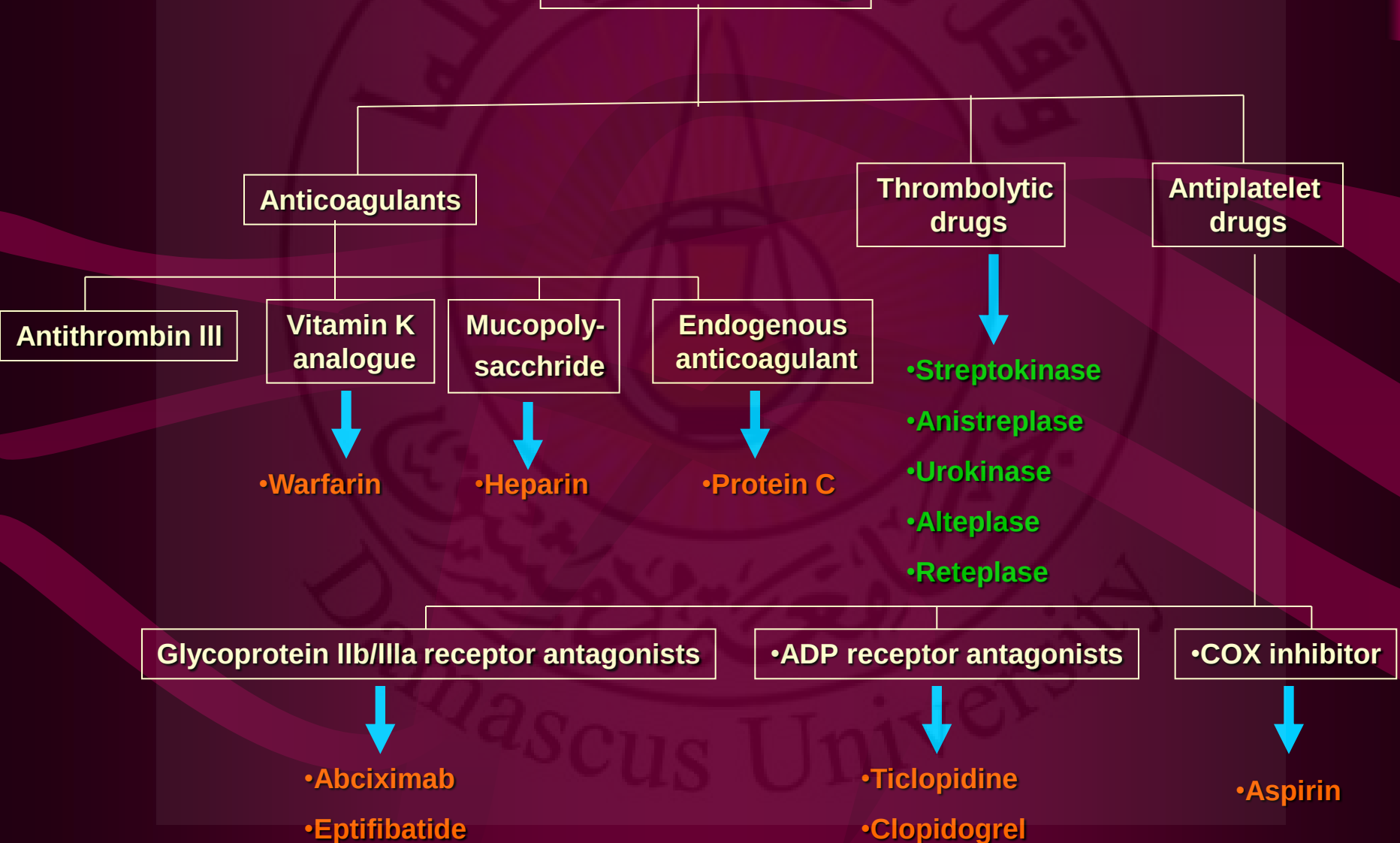


Figure 34-1. A model of the coagulation cascade, including its inhibition by the activated form of the protein C. Tissue factor (TF) is important in initiating the cascade. Tissue factor pathway inhibitor (TFPI) inhibits the action of the VIIa-TF complex. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

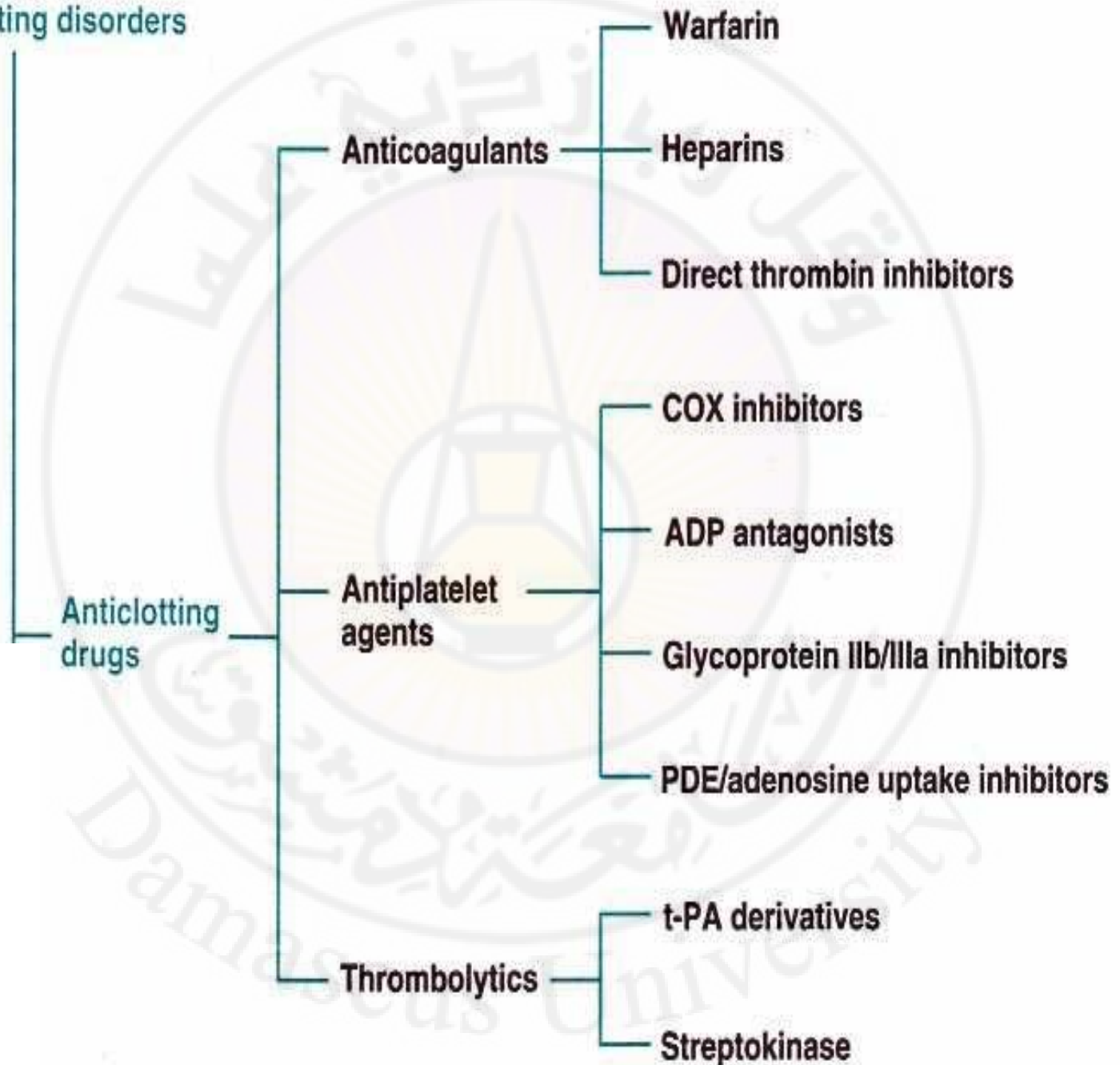
The drugs used in clotting and bleeding disorders fall into 2 primary groups: (1) drugs used in patients at risk for vascular occlusion to decrease clotting or dissolve clots already present and (2) drugs used to increase clotting in patients with clotting deficiencies. The first group, the anticlotting drugs, include some of the most commonly used drugs in the United States. Anticlotting drugs are used in the treatment of myocardial infarction and other acute coronary syndromes, atrial fibrillation, ischemic stroke, and deep vein thrombosis (DVT). The anticoagulant and thrombolytic drugs are effective in treatment of both venous and arterial thrombosis, whereas antiplatelet drugs are used primarily for treatment of arterial disease.

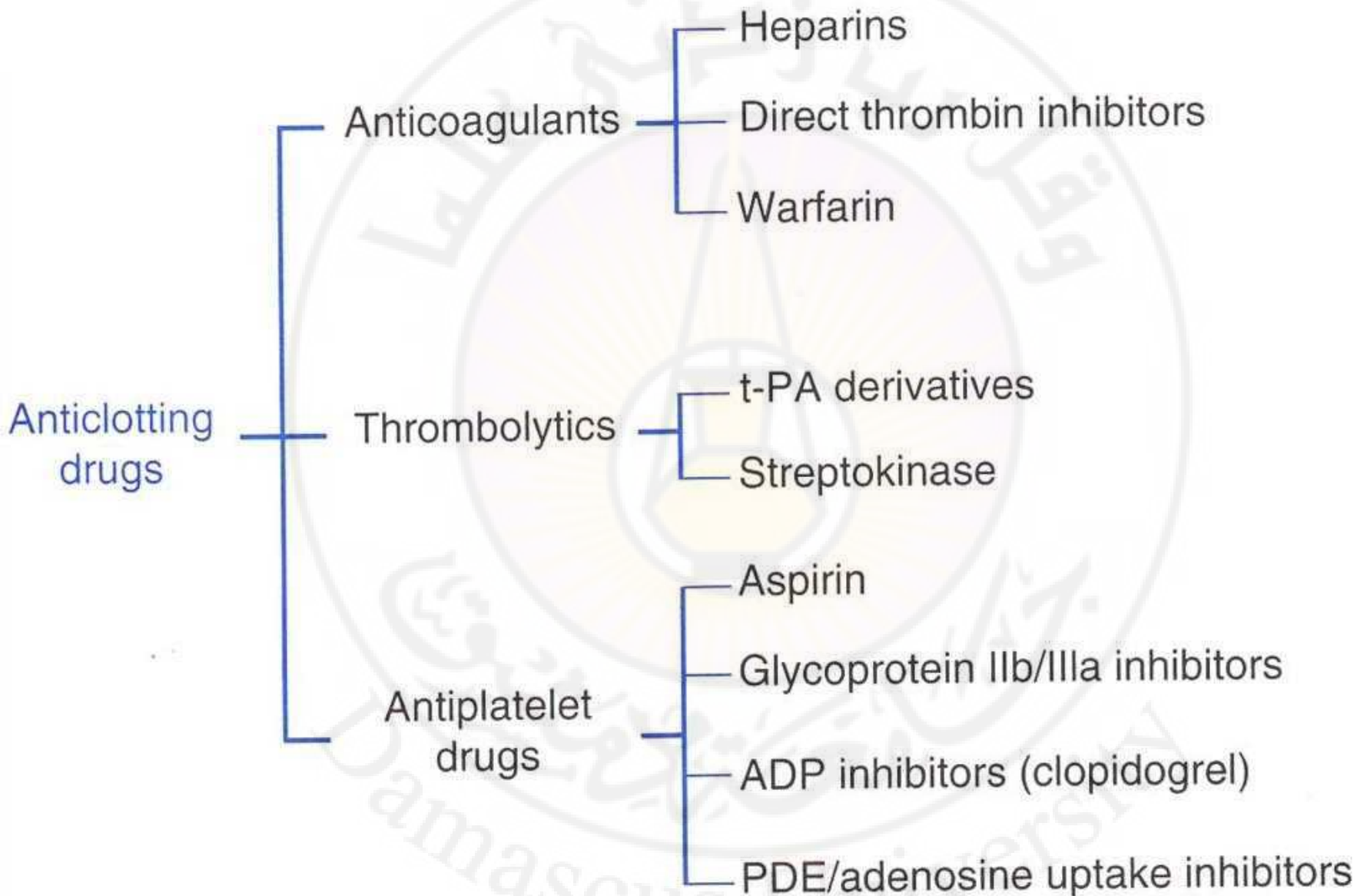
Drugs used in clotting disorders

To reduce clotting



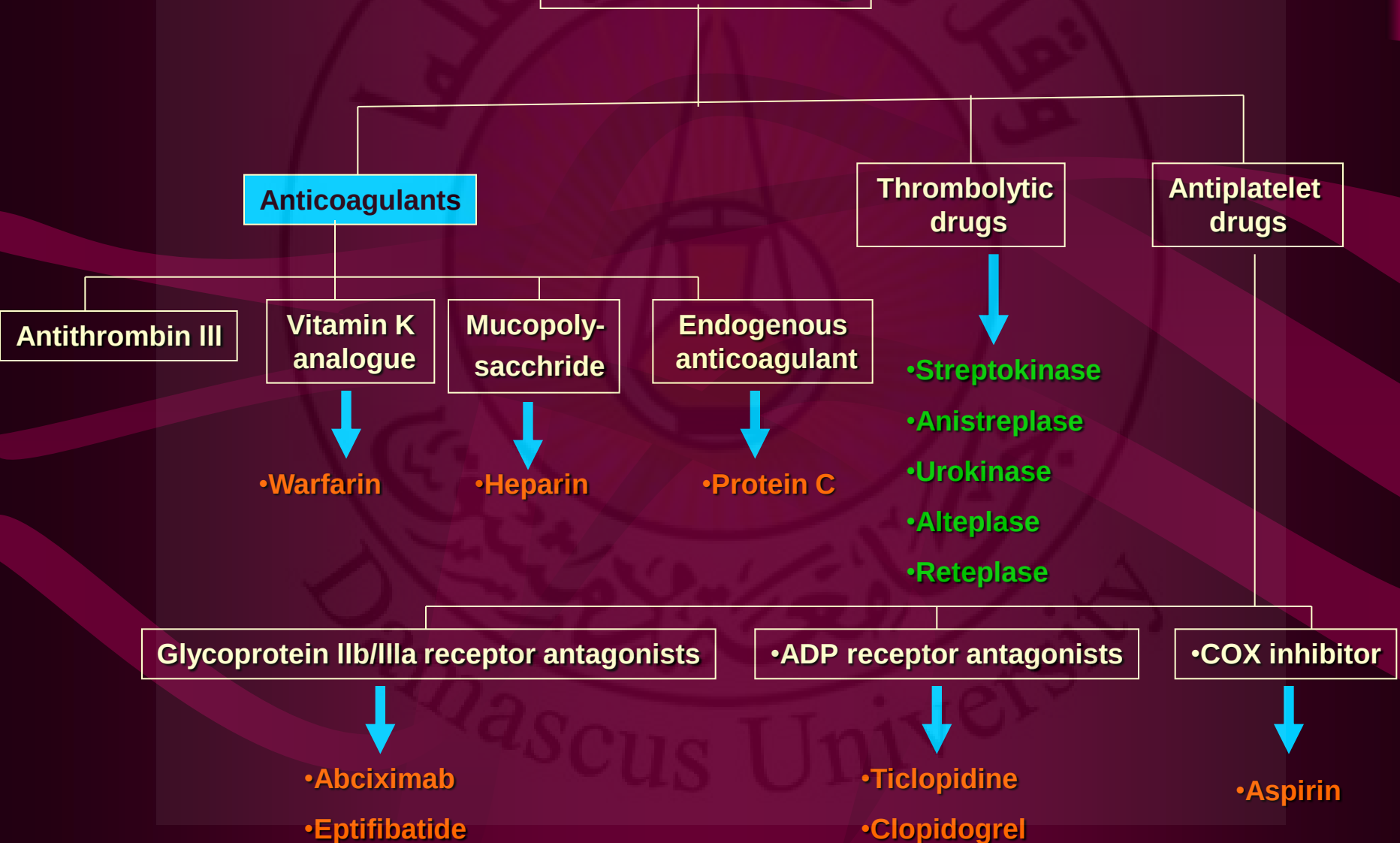
Drugs used in
clotting disorders





Drugs used in clotting disorders

To reduce clotting





❖ Warfarin

❏ **A: PO; delayed onset and effect**

❏ **M: Hepatic metabolism.**

❏ **E: Metabolites excreted in urine.**

Mechanism of action

Warfarin

- Inhibits the production of functional vitamine K depended clotting factors.**

Clinical Uses

Warfarin

- ❑ Venous thromboses.
- ❑ Pulmonary embolism.
- ❑ Prevention of thrombotic complications of atrial fibrillation or cardiac valve replacement.

Side effects

Warfarin

❖ Bleeding.

❖ Thrombosis early in therapy due to protein C deficiency teratogen.

❖ Vitamin K is reversal agent or plasma.

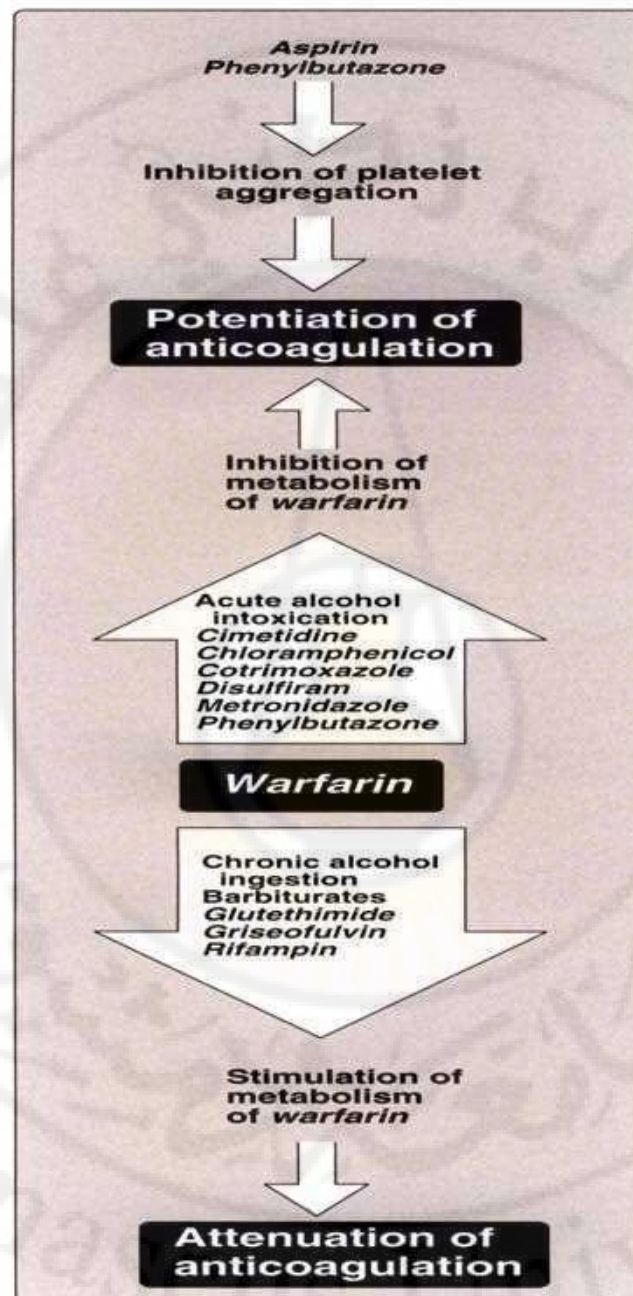


Figure 20.20
Drugs affecting the anticoagulant effect of warfarin.



❖ Heparin

❑ **A: Parenteral IV or SC.**

Mechanism of action

Heparin

- ✓ **Complexes with antithrombin III.**
- ✓ **Irreversibly in activate the coagulation factors thrombin and factor Xa.**

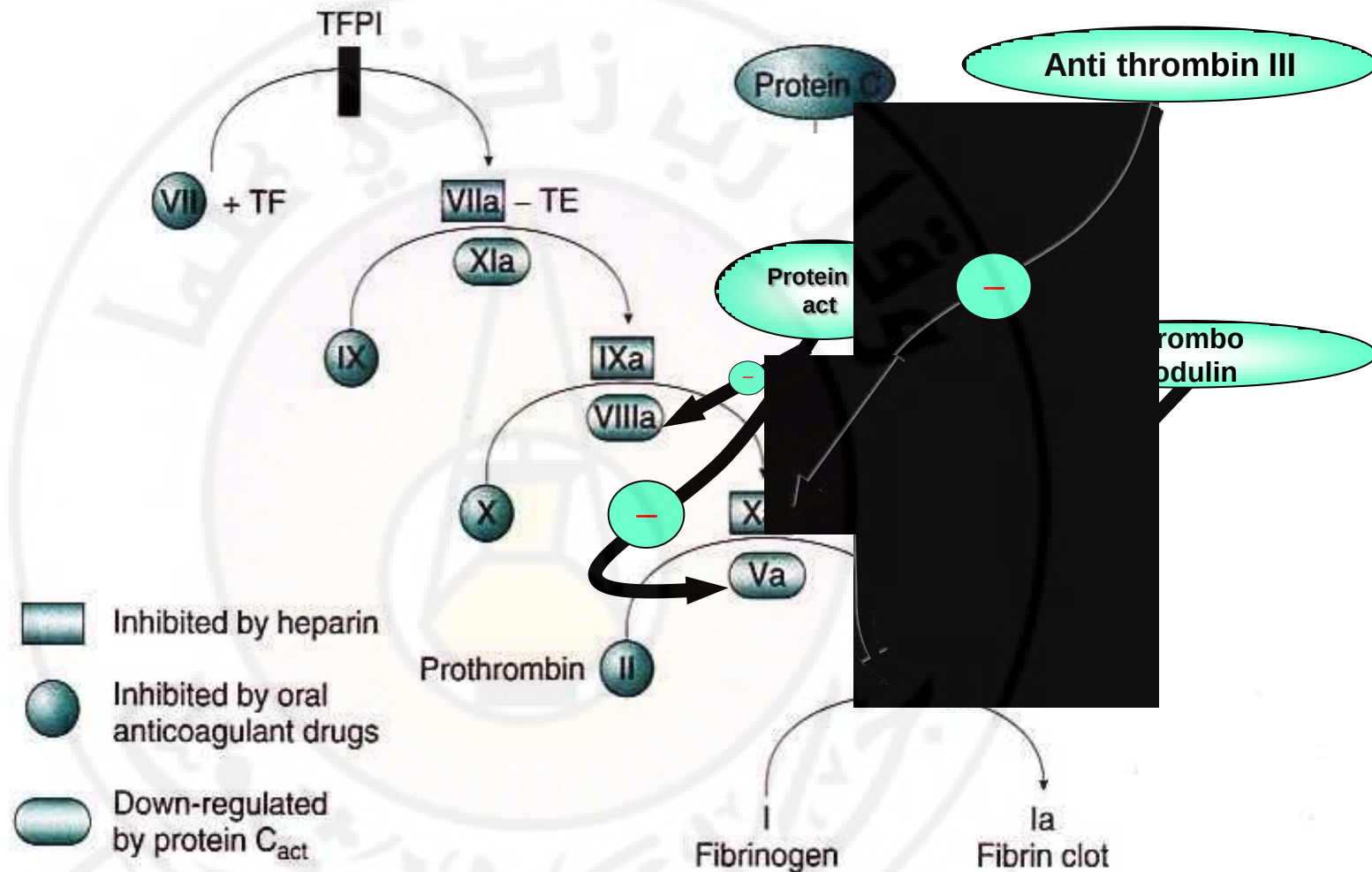


Figure 34-1. A model of the coagulation cascade, including its inhibition by the activated form of the protein C. Tissue factor (TF) is important in initiating the cascade. Tissue factor pathway inhibitor (TFPI) inhibits the action of the VIIa-TF complex. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

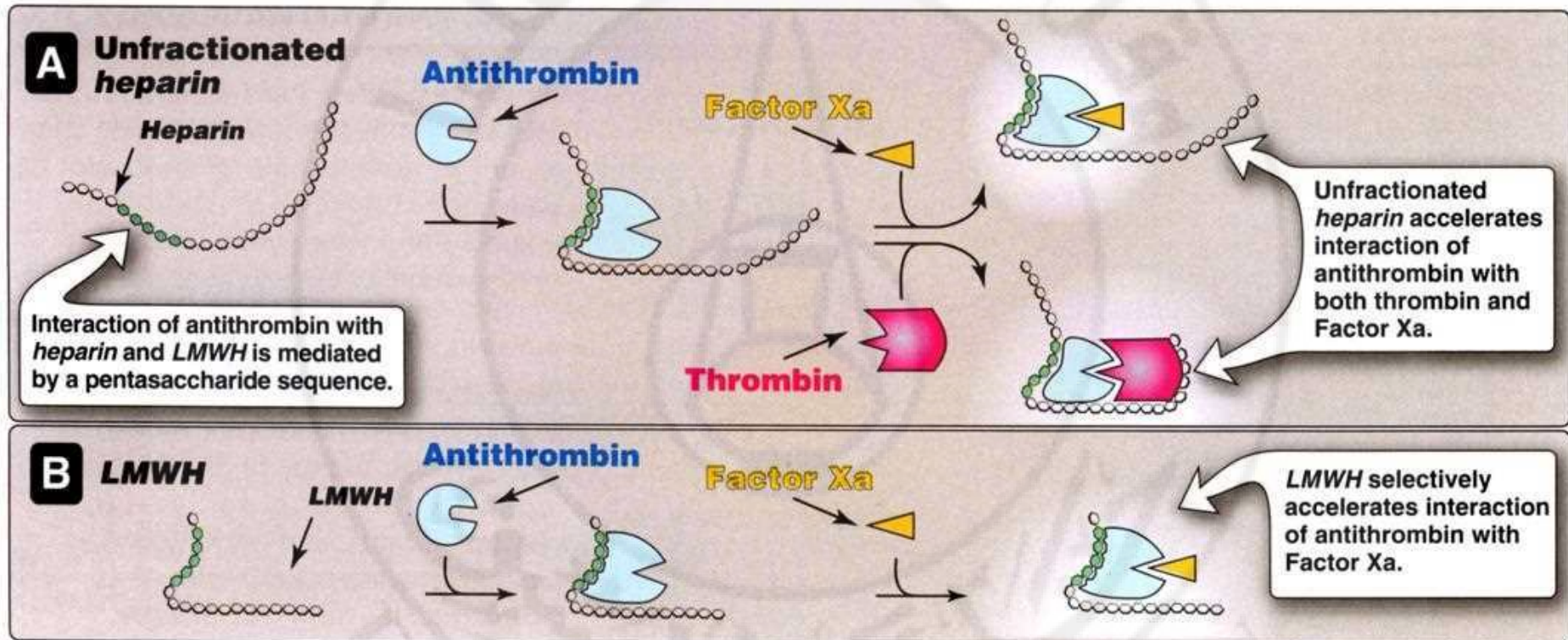


Figure 20.14

Heparin- and low-molecular-weight heparin (LMWH)-mediated inactivation of thrombin or Factor Xa.



Clinical Uses

Heparin

- ❑ Venous thromboses.
- ❑ Pulmonary embolism.
- ❑ Myocardial Infarction.
- ❑ Unstable Angina.
- ❑ Adjuvant to thrombolytics.

Side effects

Heparin

- ❖ Bleeding.
- ❖ Thrombocytopenia.
- ❖ Osteoporosis with chronic use.
- ❖ Protamine is reversal agent.

LMW-Heparins



- ➔ More selective anti-factor X activity.
- ➔ More reliable pharmacokinetics with renal elimination.
- ➔ Less risk of thrombocytopenia.



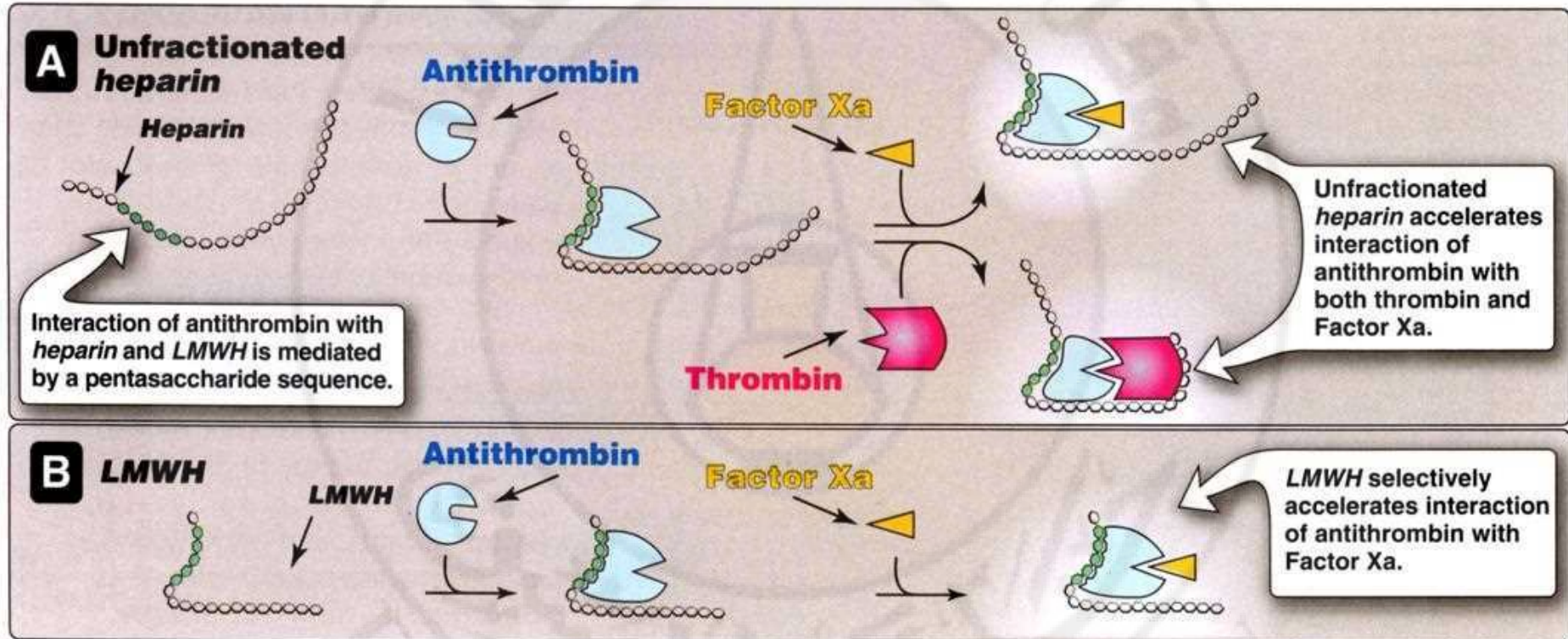


Figure 20.14

Heparin- and low-molecular-weight heparin (LMWH)-mediated inactivation of thrombin or Factor Xa.

Table 34-1. Properties of heparins and warfarin.

Property	Heparins	Warfarin
Structure	Large polymers, acidic	Small lipid-soluble molecule
Route of administration	Parenteral	Oral
Site of action	Blood	Liver
Onset of action	Rapid (seconds)	Slow, limited by half-lives of factors being replaced
Mechanism of action	Activates antithrombin III, which proteolyzes factors including thrombin and factor Xa	Impairs posttranslational modification of factors II, VII, IX, X
Monitoring	aPTT for unfractionated heparin but not LMW heparins	PT
Antidote	Protamine for unfractionated heparin but not LMW heparins	Vitamin K, plasma
Use	Mostly acute, over days	Chronic, over weeks to months
Use in pregnancy	Yes	No



❖ Lepirudin

❏ **A: IV.**

❏ **Direct Thrombin Inhibitor.**

Mechanism of action

Lepirudin

❖ **Binds to thrombin's active site and inhibit its enzymatic action.**



Clinical Uses

Lepirudin

- ❑ In patients with heparin-induced thrombocytopenia (HIT).

Side effects

Lepirudi
II

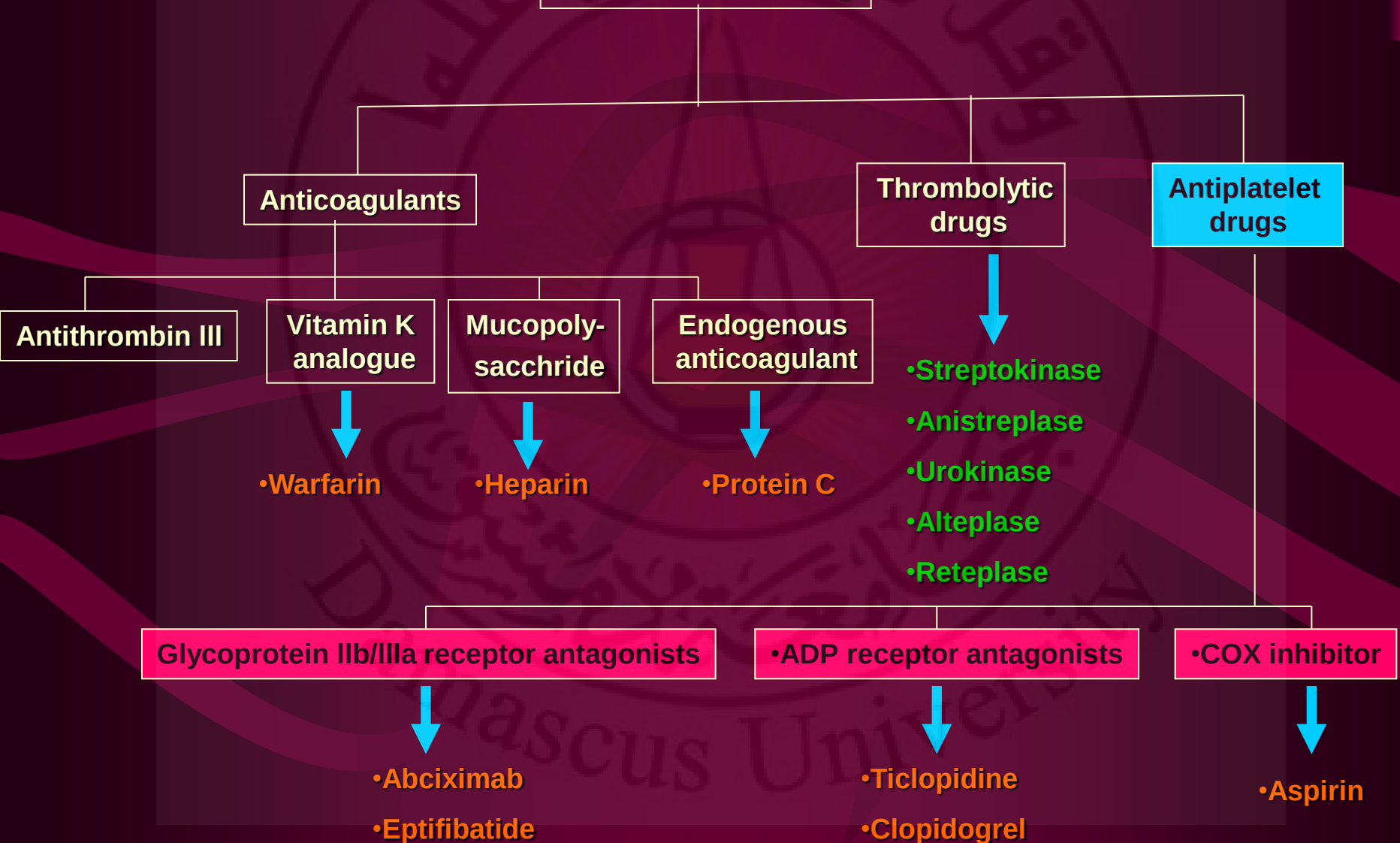
- ❖ Bleeding.
- ❖ Anaphylactic reaction.
- ❖ No reversal agent.
- ❖ Prolonged uses of lepirudin can induce formation of antibodies that form complex with lepirudin and prolong its action.

B. *Reduced anticoagulant action*

1. Barbiturates and other hypnotics (but not benzodiazepines), rifampin and griseofulvin induce the metabolism of oral anticoagulants. The dose of anticoagulant determined during therapy with these drugs would be higher: if the same is continued after withdrawing the inducer—marked hypoprothrombinemia can occur—fatal bleeding is on record.
2. Oral contraceptives: increase blood levels of clotting factors.

Drugs used in clotting disorders

To reduce clotting



A. CLASSIFICATION AND PROTOTYPES

Antiplatelet drugs include **aspirin** and other NSAIDs, glycoprotein IIb/IIIa receptor inhibitors (**abciximab**, **tirofiban**, and **eptifibatide**), antagonists of ADP receptors (**clopidogrel** and **ticlopidine**), and inhibitors of phosphodiesterase 3 (**dipyridamole** and **cilostazol**) (Figure 34–3).



❖ Aspirin

- ❑ **A:** PO.
- ❑ **M:** Extensive first- pass hepatic metabolism.
- ❑ **E:** Metabolites excreted in urine.

Mechanism of action

Aspirin

❖ **Prevents activation of thromboxane A_2
(a potent stimulator of platelet aggregation)
by irreversibly binding to COX.**

Side effects

Aspirin

- ❖ Excessive bleeding.
- ❖ GI bleeding.
- ❖ PUD.



❖ Ticlopidine

- ❑ **A: PO; well absorbed.**
- ❑ **M: Hepatic metabolism.**
- ❑ **E: Metabolites excreted in urine and feces.**



❖ Clopidogrel

❏ **A: PO.**

❏ **M: Hepatic metabolism to active metabolites.**

❏ **E: Metabolites excreted in urine and feces.**

Mechanism of action

Ticlopidine & Clopidogrel

❖ **Irreversible inhibition of ADP- mediated platelet aggregation.**

Side effects

Ticlopidine

- ❖ Excessive bleeding.
- ❖ Nausea.
- ❖ Dyspepsia.
- ❖ Diarrhea.
- ❖ Sever neutropenia (rare).
- ❖ Thrombotic thrombocytopenic purpura.

Side effects

Clopidogrel

- ❖ Fewer side effects than Ticlopidine
- ❖ Thrombotic thrombocytopenic purpura.



❖ Abciximab

❏ **A: IV.**

❏ **E: Rapidly cleared from blood**

(likely secondary to rapid receptor binding).

Mechanism of action

Abciximab

✓ **Human monoclonal antibody directed against the glycoprotein IIb/ IIIa complex..**



❖ Eptifibatide

❏ **A: IV.**

❏ **E: Parent drug and products of its breakdown excreted in urine.**

Mechanism of action

Eptifibatide

✦ **Reversible blockade of glycoprotein IIb/ IIIa receptor..**

Side effects

Abciximab & Eptifibatide

- ❖ Excessive bleeding.
- ❖ Thrombocytopenia with LTU.

Dipyridamole and the newer cilostazol appear to have a dual mechanism of action. They prolong the platelet-inhibiting action of intracellular cAMP by inhibiting phosphodiesterase 3, an enzyme that degrades cAMP. They also inhibit the uptake of adenosine by endothelial cells and erythrocytes and thereby increase the plasma concentration of adenosine. Adenosine acts through platelet adenosine A_2 receptors to increase platelet cAMP and inhibit aggregation.

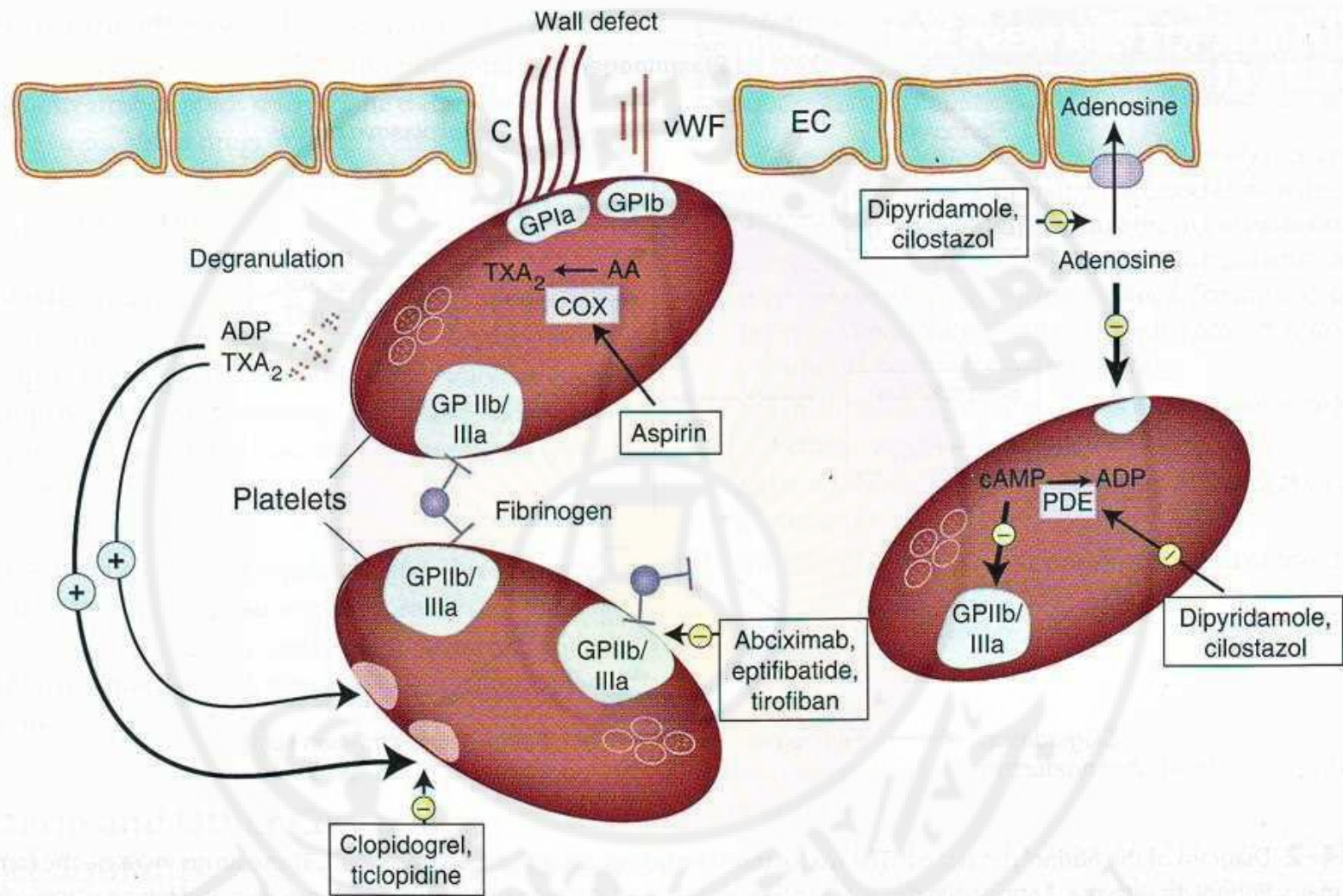


FIGURE 34–3 Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and GP IIb/IIIa, which binds fibrinogen and other macromolecules. Antiplatelet prostacyclin (PGI₂) is released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A₂ (TXA₂), and serotonin (5-HT). (Modified and reproduced, with permission, from Katzung BG, Masters SB, and Trevor AT editors: *Basic & Clinical Pharmacology*, 11th ed. McGraw-Hill, 2009: Fig. 34–1.)

thrombosis

Ticlopidine: Older ADP receptor antagonist with more toxicity, particularly leukopenia and thrombotic thrombocytopenic purpura

Dipyridamole

Dipyridamole

Inhibits adenosine uptake and inhibits phosphodiesterase enzymes that degrade cyclic nucleotides (cAMP, cGMP)

Prevention of thromboembolic complications of cardiac valve replacement; combined with aspirin for secondary prevention of ischemic stroke

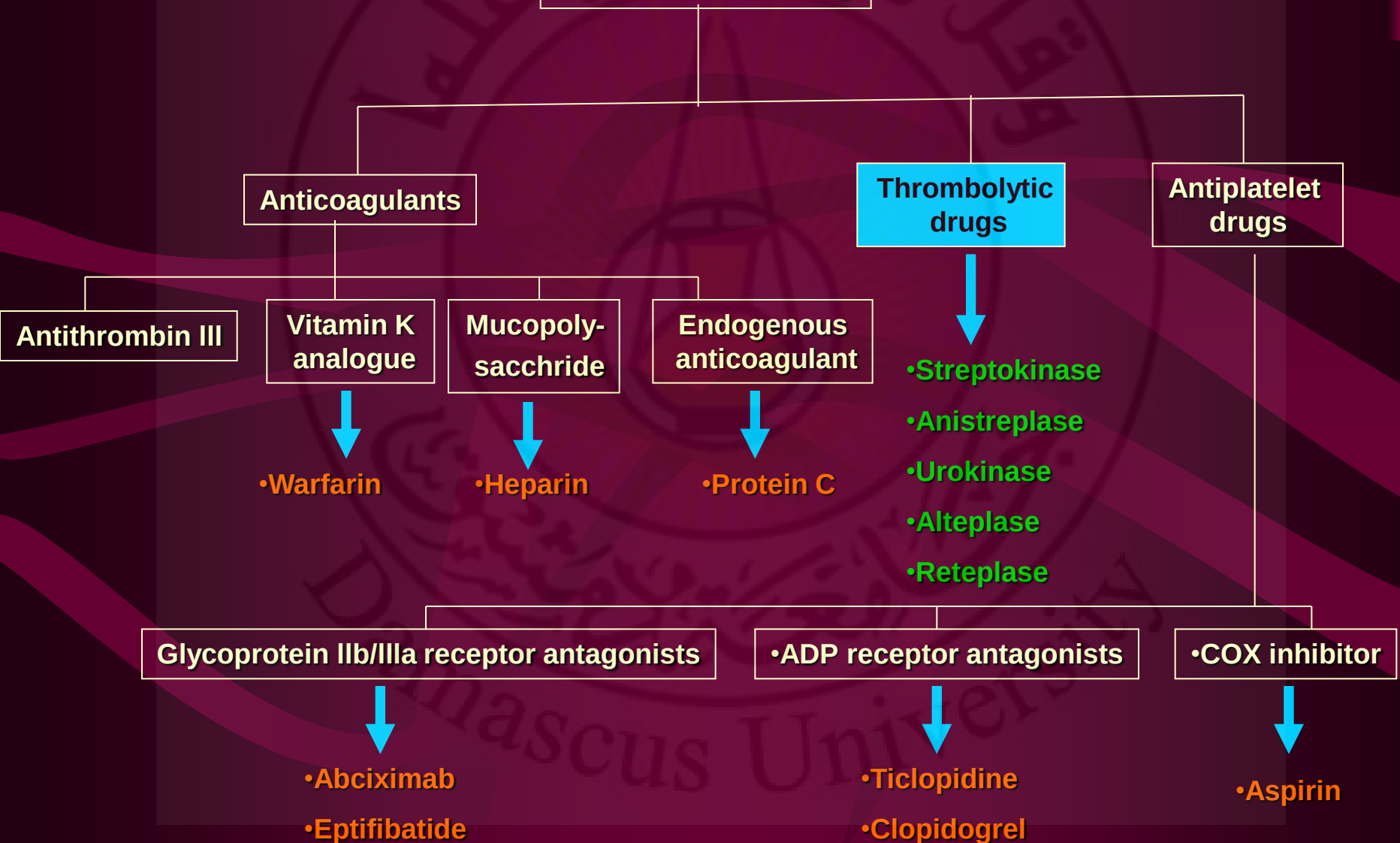
Oral administration

Headache, palpitations, contraindicated in congestive heart failure

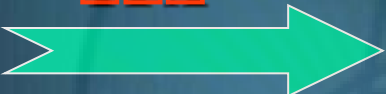
Damascus University

Drugs used in clotting disorders

To reduce clotting



Thrombolytic Agents

Plasminogen  *Plasmin*  *Fibrin*

Fibrinolysis

Pharmacokinetics

Streptokinase

❑ **A: IV.**

❑ **M: Cleared from blood by antibodies and reticuloendothelial system.**

Mechanism of action

Streptokinase

- Protein from *Streptococcus* that converts plasminogen to plasmin.
- Plasmin then functions to break up the clot by dissolving fibrin.

Side effects



- ➔ **Excessive bleeding.**
- ➔ **Cerebral hemorrhage.**
- ➔ **Fever, allergic reactions, and therapeutic resistance in patients with streptococcal antibodies.**

Pharmacokinetics

Anistreplase

❏ **A: IV.**

❏ **M: Breaks down into components following administration.**

Mechanism of action

Anistreplase

- Human plasminogen and bacterial streptokinase that has been acylated to protect the enzyme' active site.

Side effects



- ➔ **Excessive bleeding.**
- ➔ **Cerebral hemorrhage.**

Pharmacokinetics

Urokinase

- ❏ **A: IV.**
- ❏ **M: Rapidly cleared from blood.**
- ❏ **E: Small amount excreted in urine and feces.**

Mechanism of action

Urokinase

- Human enzyme produced by the kidney that converts plasminogen to plasmin.
- Plasmin then functions to break up the clot by dissolving fibrin.

Pharmacokinetics

Alteplase

- ❑ **A: IV.**
- ❑ **M: Principally cleared by liver.**
- ❑ **E: In urine.**

Pharmacokinetics

Reteplase

❏ **A: IV.**

❏ **E: Cleared by kidneys and liver.**

Mechanism of action

Reteplase

- Human t- PA from which several amino acids have been deleted..
- Converts fibrin- bound plasminogen to plasmin (clot selective).

Patients with chronic atrial fibrillation, a common supraventricular arrhythmia, routinely receive warfarin to prevent the formation of blood clots in the poorly contracting atrium and to decrease the risk of embolism of such clots to the brain or other tissues. Such patients are also often treated with antiarrhythmic drugs. The primary goals of antiarrhythmic treatment are to slow the atrial rate and, most importantly, control the ventricular rate.

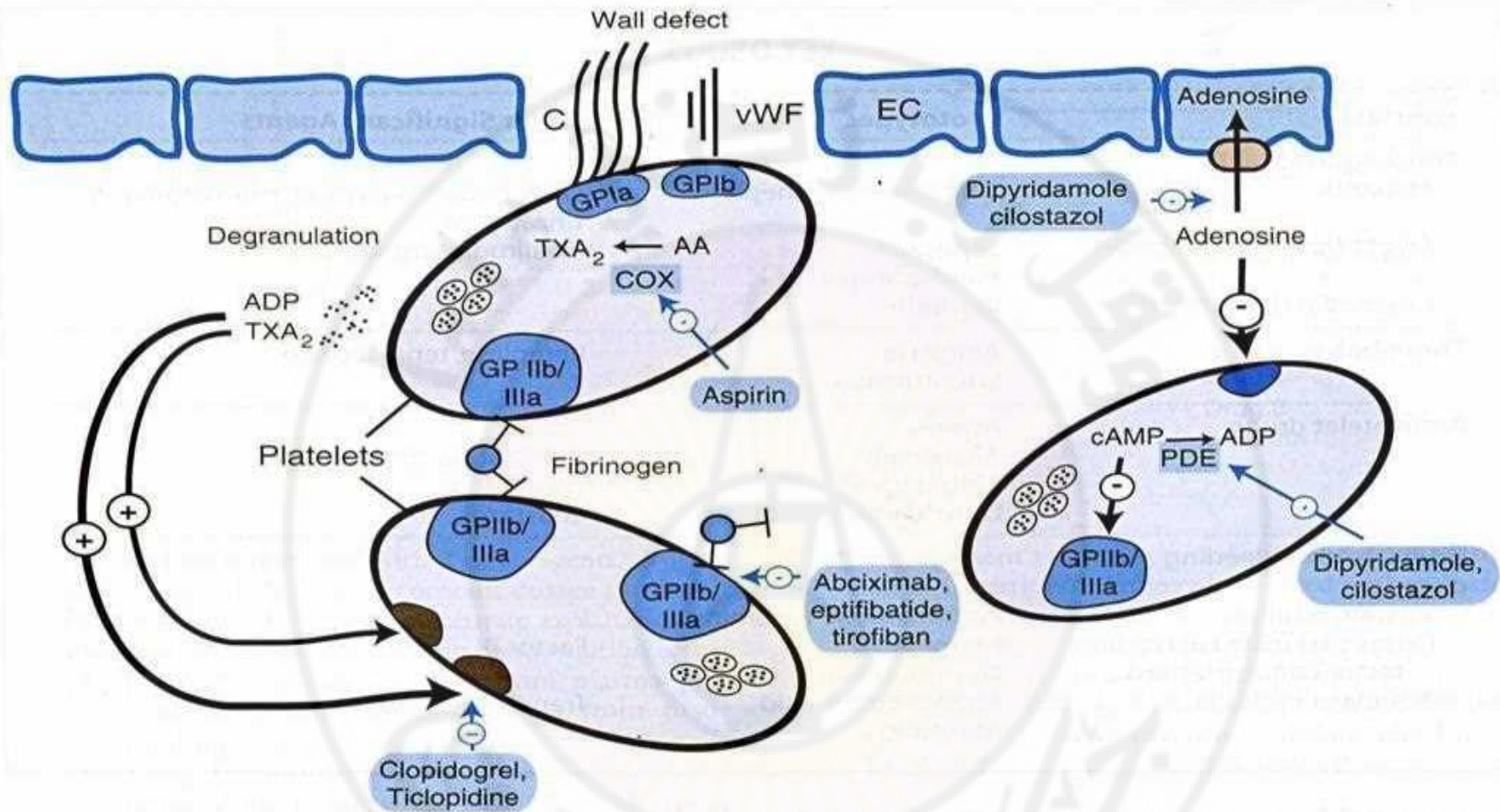


Figure 34–3. Antiplatelet drug mechanisms. At the site of blood vessel wall defects and damage endothelial cells (EC), the exposure of collagen (C) and von Willebrand factor (vWF) activates platelets by binding to platelet membrane glycoproteins (GP) 1a and 1b. Platelet activation triggers degranulation and the release of adenosine diphosphate (ADP) and thromboxane A₂ (TXA₂), which act through platelet receptors to modify GPIIb/IIIa so it is able to bind fibrinogen and cross-link platelets. Aspirin inhibits the production of TXA₂ by irreversibly inhibiting cyclooxygenase (COX). Abciximab, eptifibatide, and tirofiban inhibit the binding of GPIIb/IIIa to fibrinogen, while clopidogrel and ticlopidine irreversibly inhibit the ADP receptor. Dipyridamole and cilostazol inhibit GPIIb/IIIa activation by inhibiting the phosphodiesterase enzyme (PDE) that degrades cAMP and by inhibiting the uptake by EC of adenosine, an endogenous inhibitor of platelet function. (Redrawn and reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 10th ed. McGraw-Hill, 2007.)

I, II, III, IV

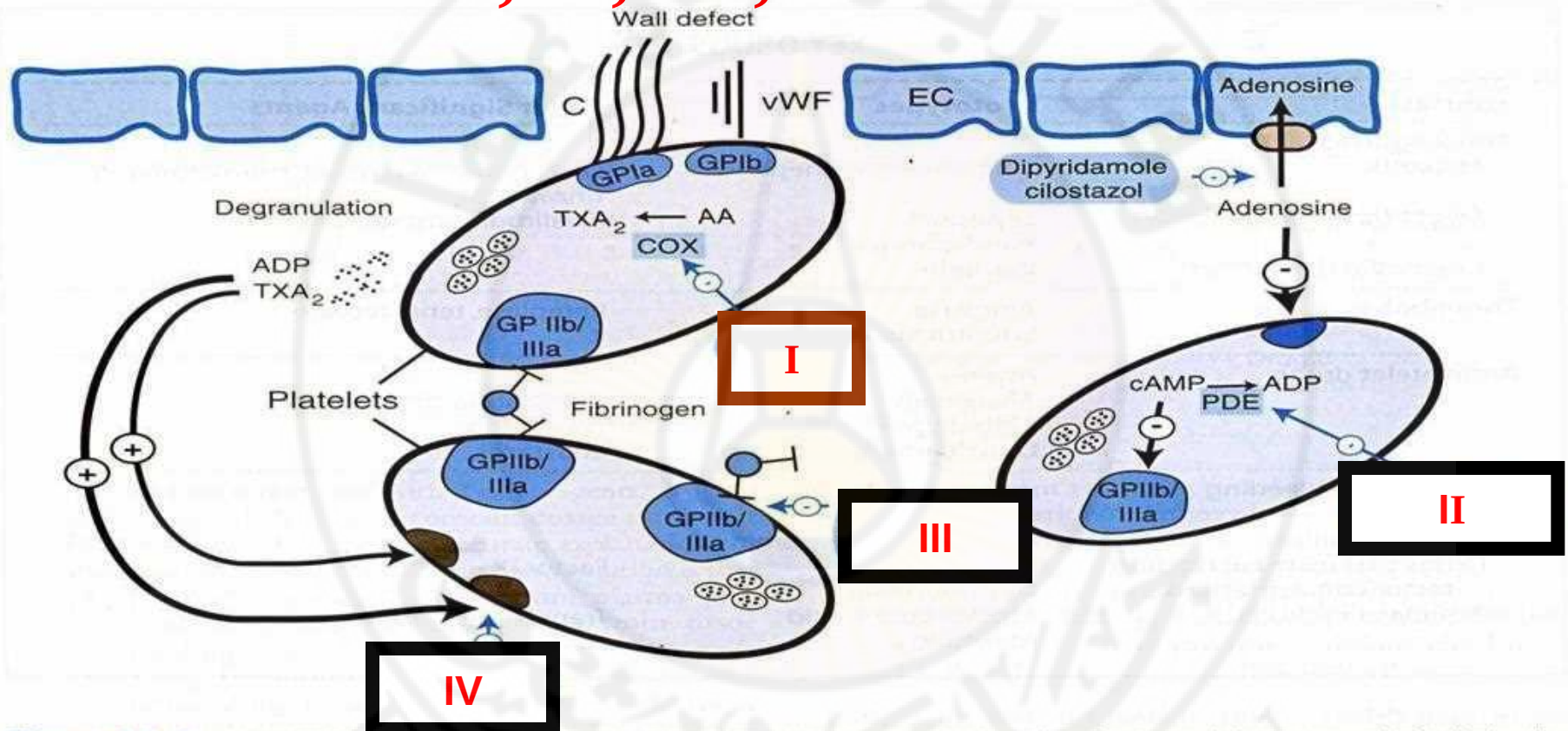


Figure 34–3. Antiplatelet drug mechanisms. At the site of blood vessel wall defects and damage endothelial cells (EC), the exposure of collagen (C) and von Willebrand factor (vWF) activates platelets by binding to platelet membrane glycoproteins (GP) 1a and 1b. Platelet activation triggers degranulation and the release of adenosine diphosphate (ADP) and thromboxane A₂ (TXA₂), which act through platelet receptors to modify GPIIb/IIIa so it is able to bind fibrinogen and cross-link platelets. Aspirin inhibits the production of TXA₂ by irreversibly inhibiting cyclooxygenase (COX). Abciximab, eptifibatide, and tirofiban inhibit the binding of GPIIb/IIIa to fibrinogen, while clopidogrel and ticlopidine irreversibly inhibit the ADP receptor. Dipyridamole and cilostazol inhibit GPIIb/IIIa activation by inhibiting the phosphodiesterase enzyme (PDE) that degrades cAMP and by inhibiting the uptake by EC of adenosine, an endogenous inhibitor of platelet function. (Redrawn and reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 10th ed. McGraw-Hill, 2007.)

To facilitate clotting

```
graph TD; A["To facilitate clotting"] --> B["Antiplasmin drugs"]; A --> C["Clotting factors"]; A --> D["Vitamin K"]; B --> E["• Aminocaproic acid"];
```

***Antiplasmin
drugs***

***Clotting
factors***

***Vitamin
K***

- **Aminocaproic acid**



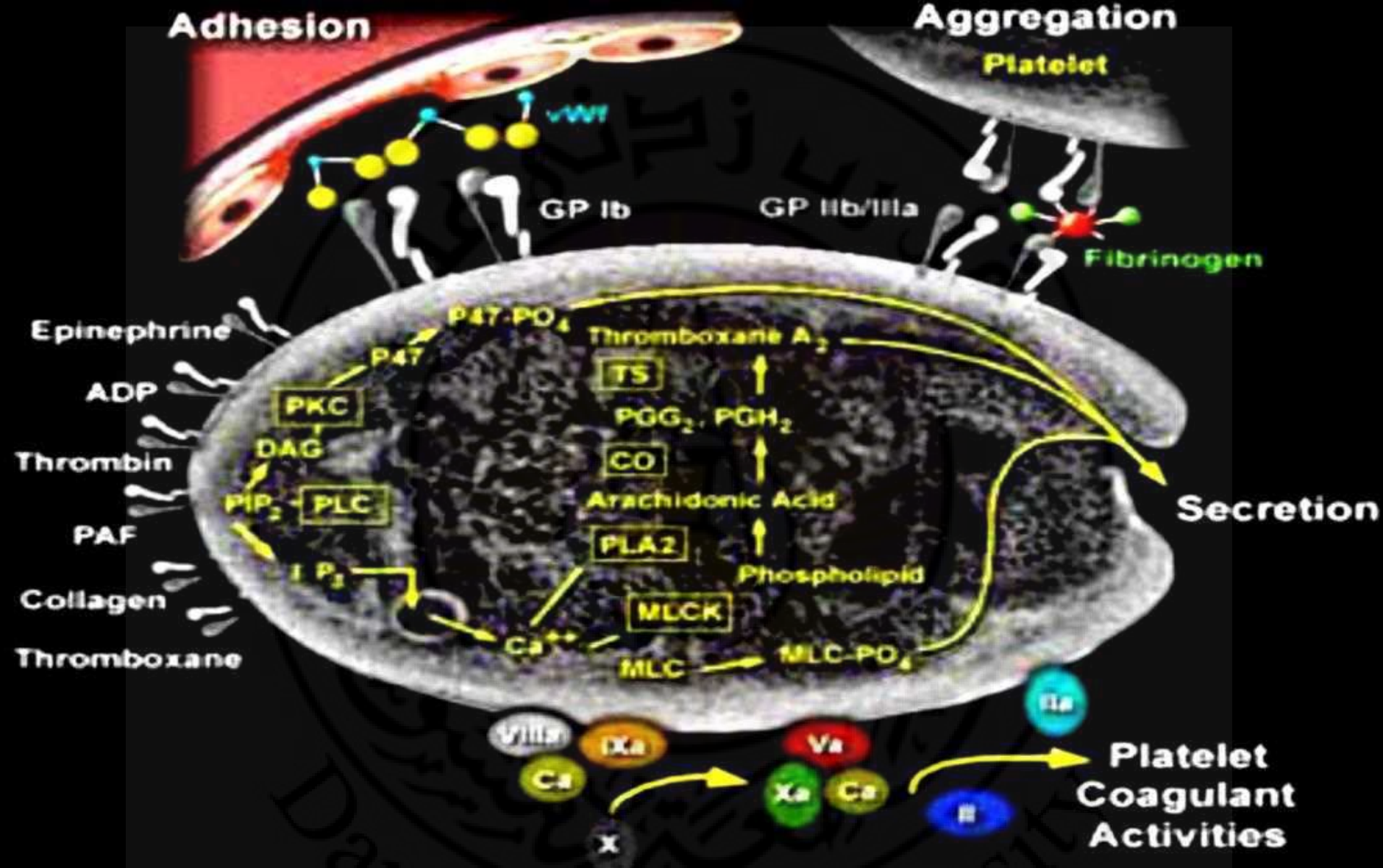
Coronary Heart Disease (CHD)

Antianginal Drugs

Management of Myocardial Infarction

Antihyperlipidemic Drugs

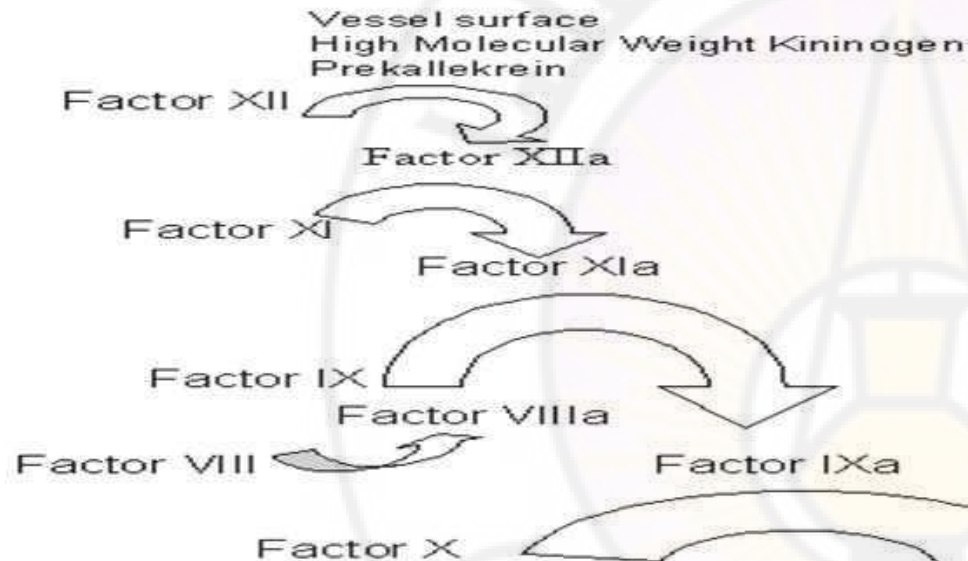
Drugs affecting Coagulation

Adhesion**Aggregation****Platelet****Fibrinogen****Secretion****Platelet
Coagulant
Activities**

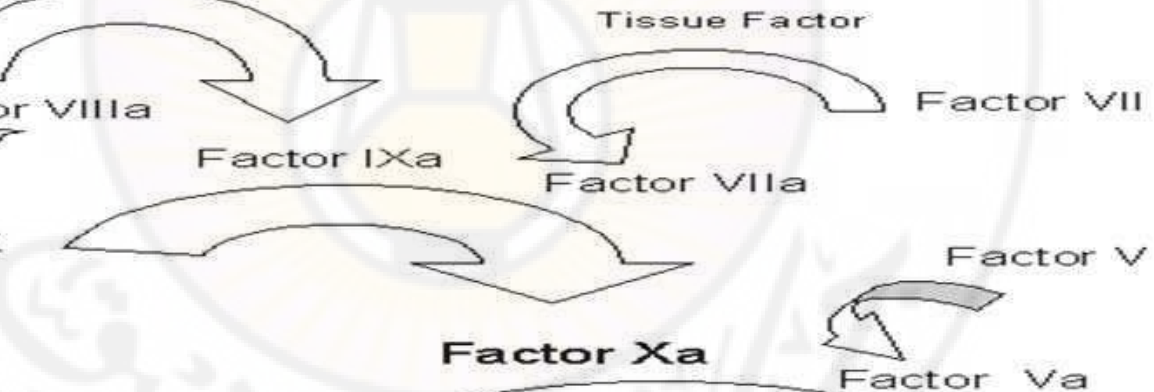
Source: Adapted from Colman RW, et al. In Colman RW, et al, eds. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. Philadelphia J.D. Lippincott Co., 1994:3.

The Classic Cascade

Intrinsic System



Extrinsic System

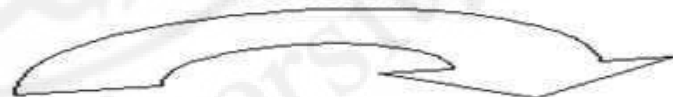


Prothrombin



Thrombin

Fibrinogen



Fibrin

Crosslinked Fibrin

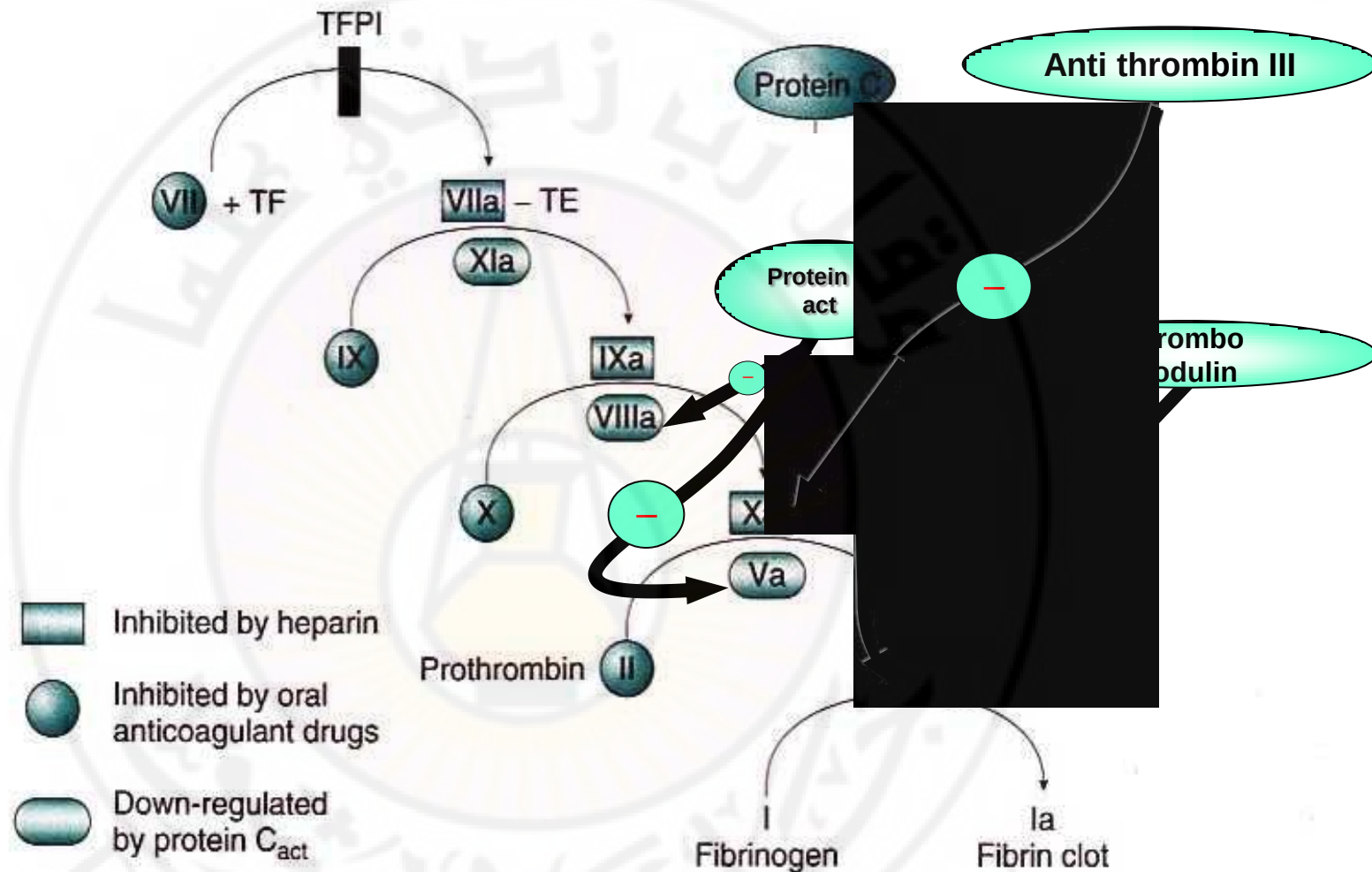
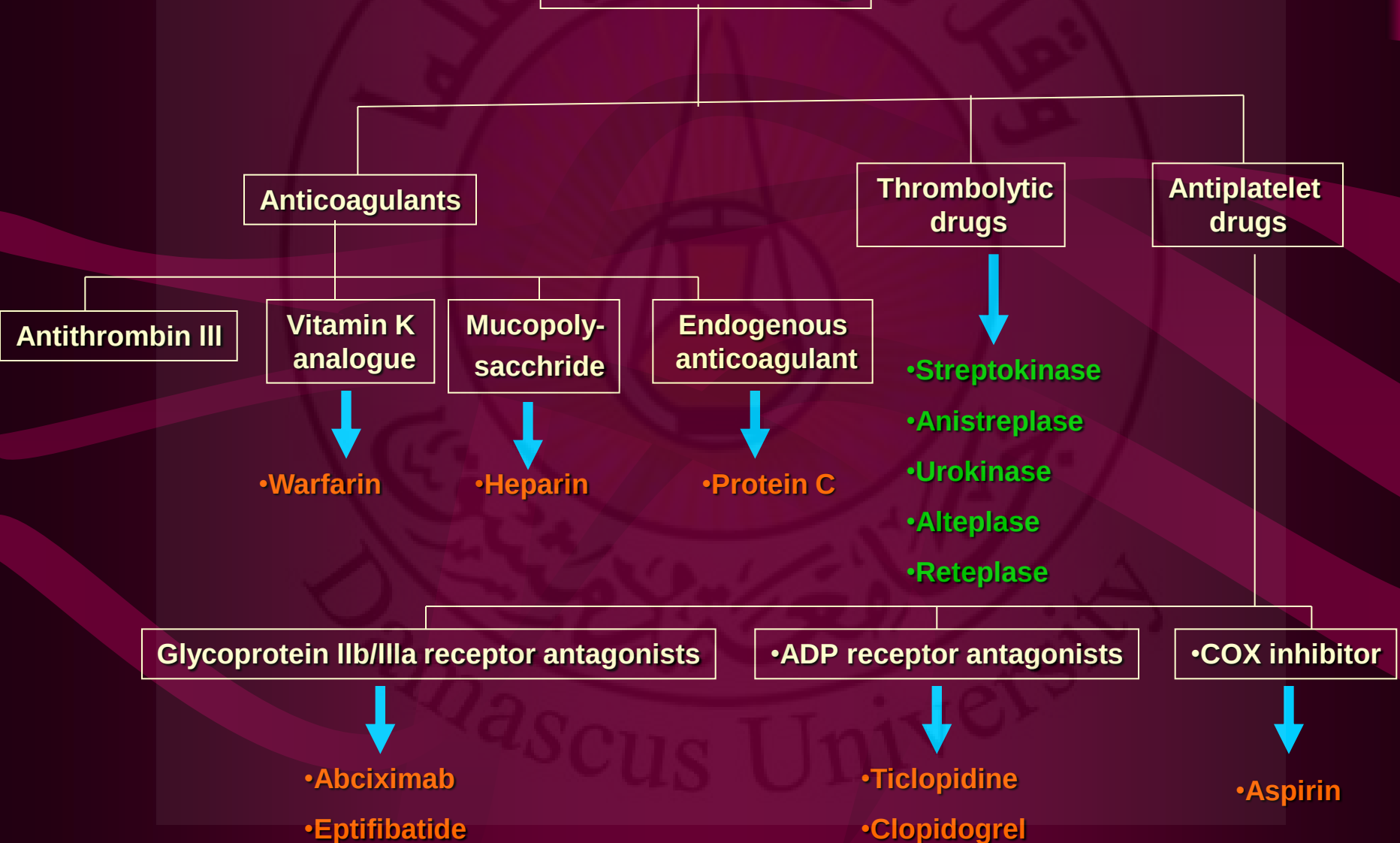


Figure 34-1. A model of the coagulation cascade, including its inhibition by the activated form of the protein C. Tissue factor (TF) is important in initiating the cascade. Tissue factor pathway inhibitor (TFPI) inhibits the action of the VIIa-TF complex. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

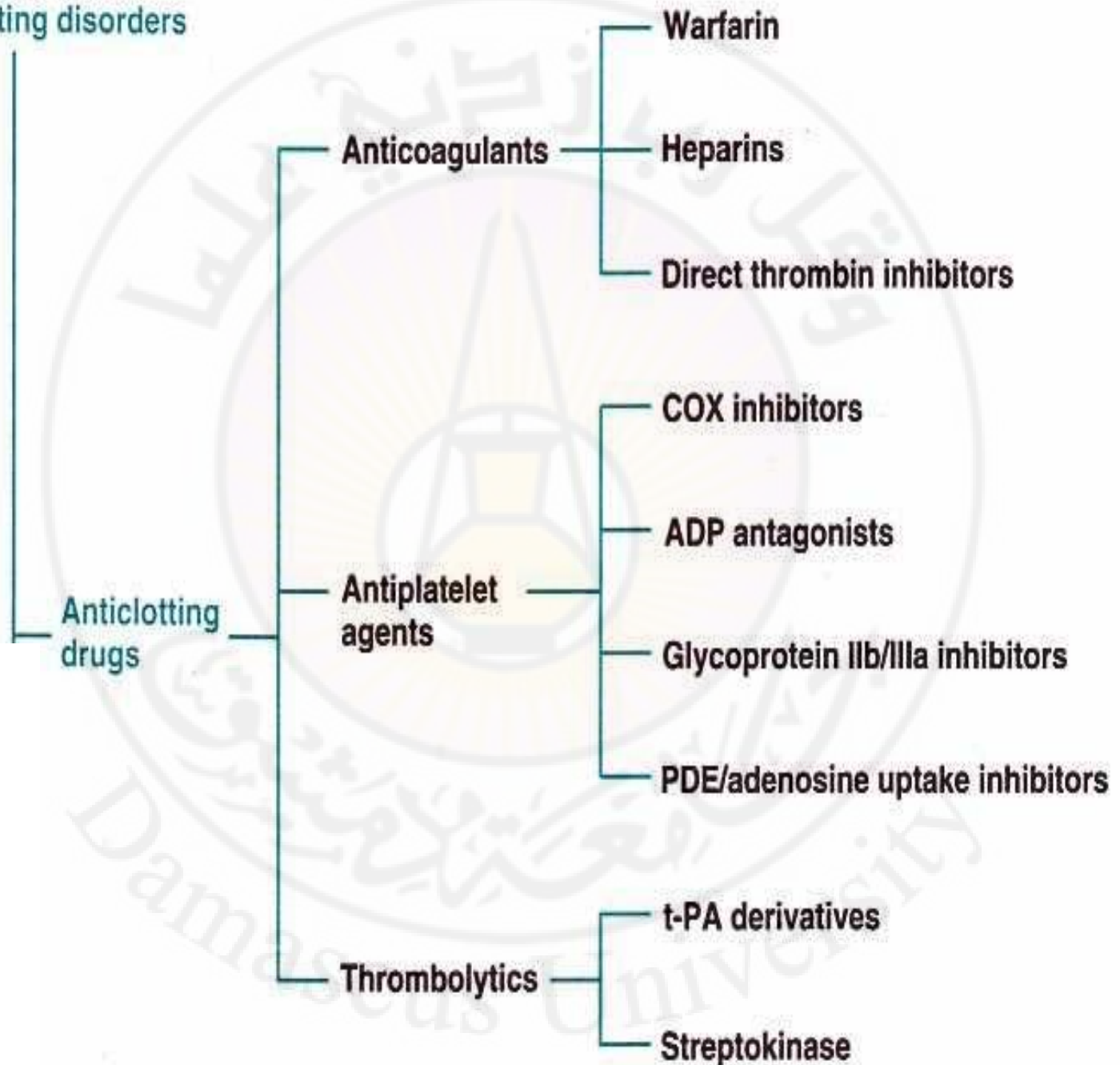
The drugs used in clotting and bleeding disorders fall into 2 primary groups: (1) drugs used in patients at risk for vascular occlusion to decrease clotting or dissolve clots already present and (2) drugs used to increase clotting in patients with clotting deficiencies. The first group, the anticlotting drugs, include some of the most commonly used drugs in the United States. Anticlotting drugs are used in the treatment of myocardial infarction and other acute coronary syndromes, atrial fibrillation, ischemic stroke, and deep vein thrombosis (DVT). The anticoagulant and thrombolytic drugs are effective in treatment of both venous and arterial thrombosis, whereas antiplatelet drugs are used primarily for treatment of arterial disease.

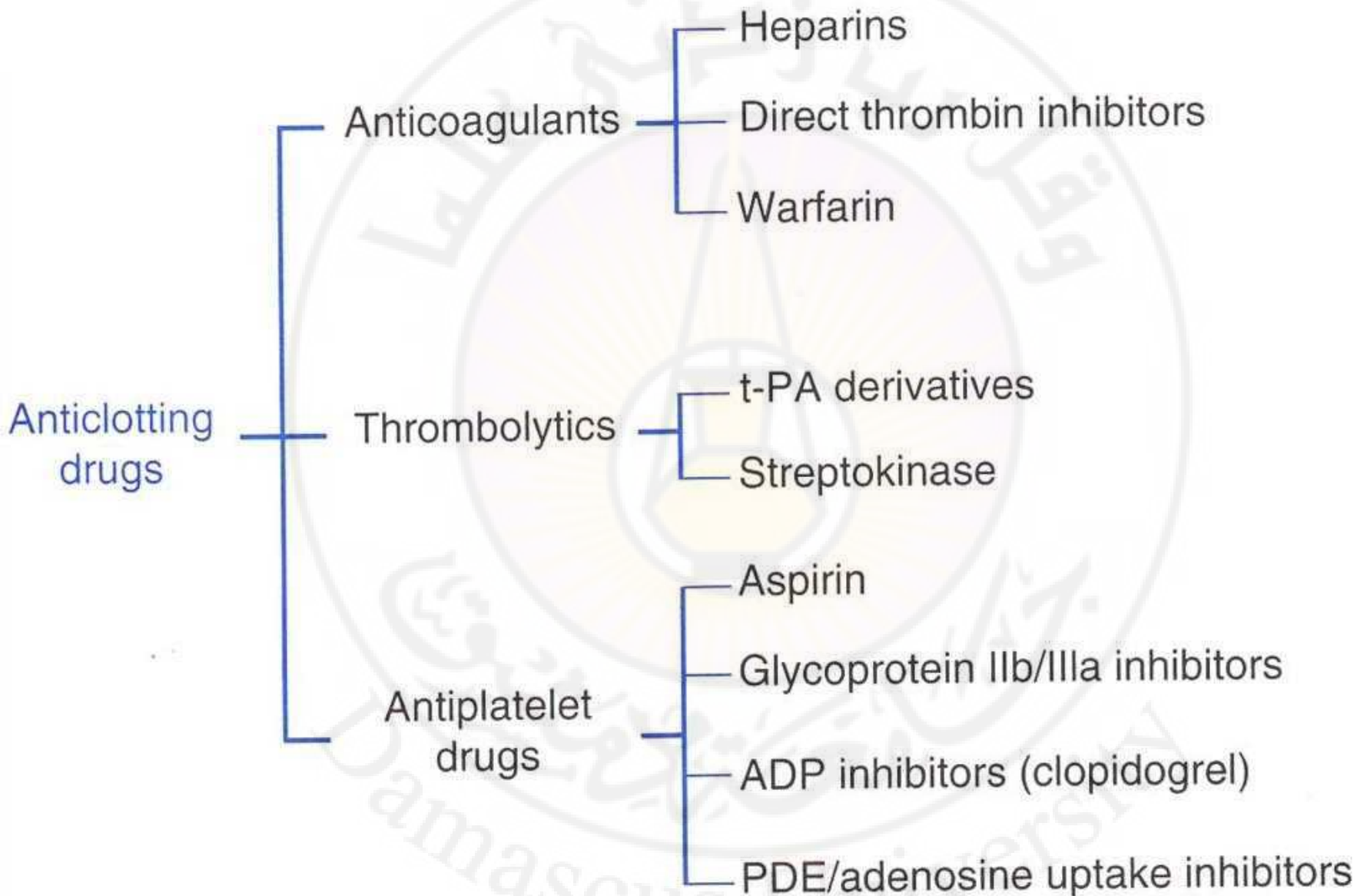
Drugs used in clotting disorders

To reduce clotting



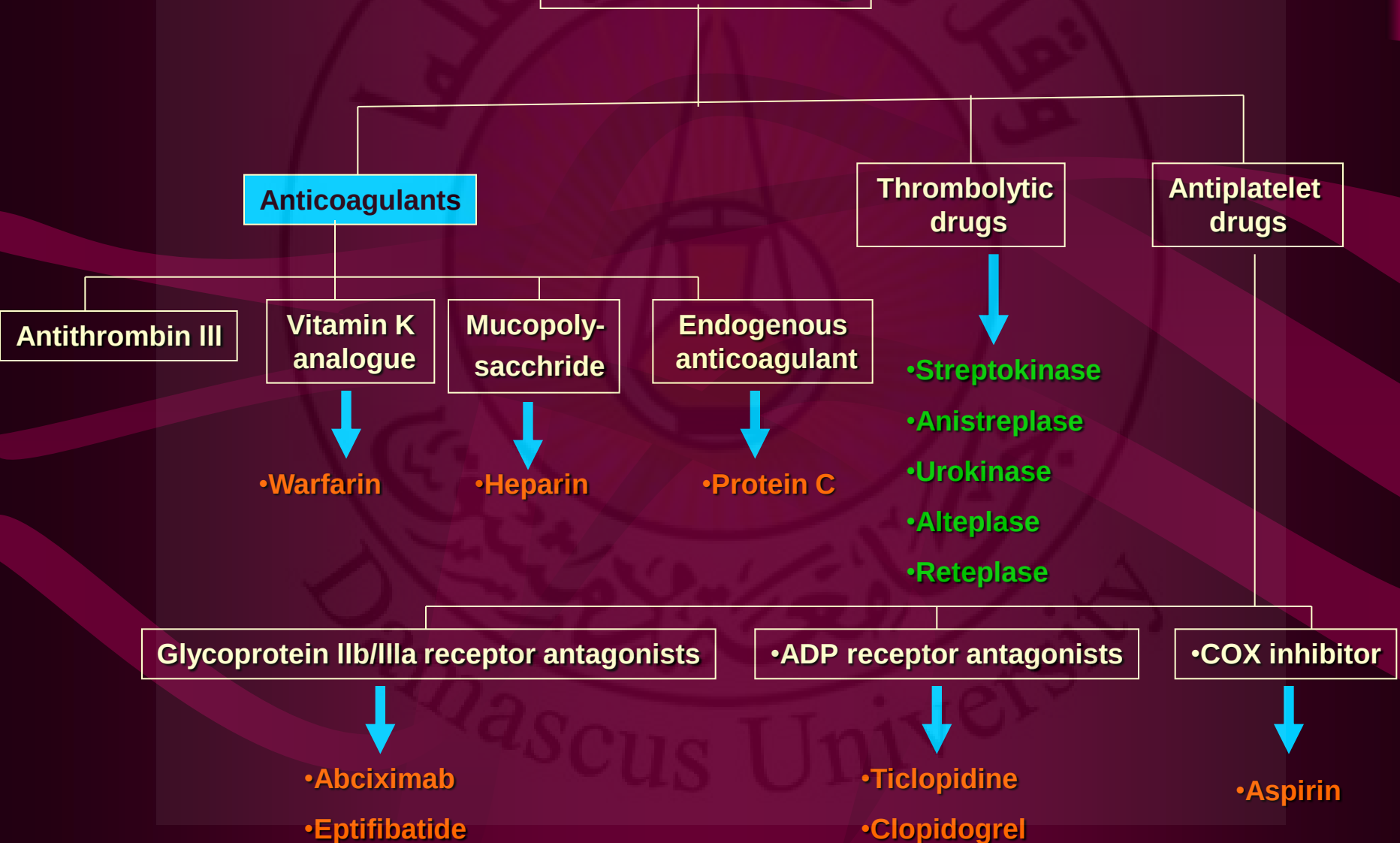
Drugs used in
clotting disorders





Drugs used in clotting disorders

To reduce clotting





❖ Warfarin

❑ **A: PO; delayed onset and effect**

❑ **M: Hepatic metabolism.**

❑ **E: Metabolites excreted in urine.**

Mechanism of action

Warfarin

- ✓ **Inhibits the production of functional vitamine K depended clotting factors.**

Clinical Uses

Warfarin

- ❑ Venous thromboses.
- ❑ Pulmonary embolism.
- ❑ Prevention of thrombotic complications of atrial fibrillation or cardiac valve replacement.

Side effects

Warfarin

❖ Bleeding.

❖ Thrombosis early in therapy due to protein C deficiency teratogen.

❖ Vitamin K is reversal agent or plasma.

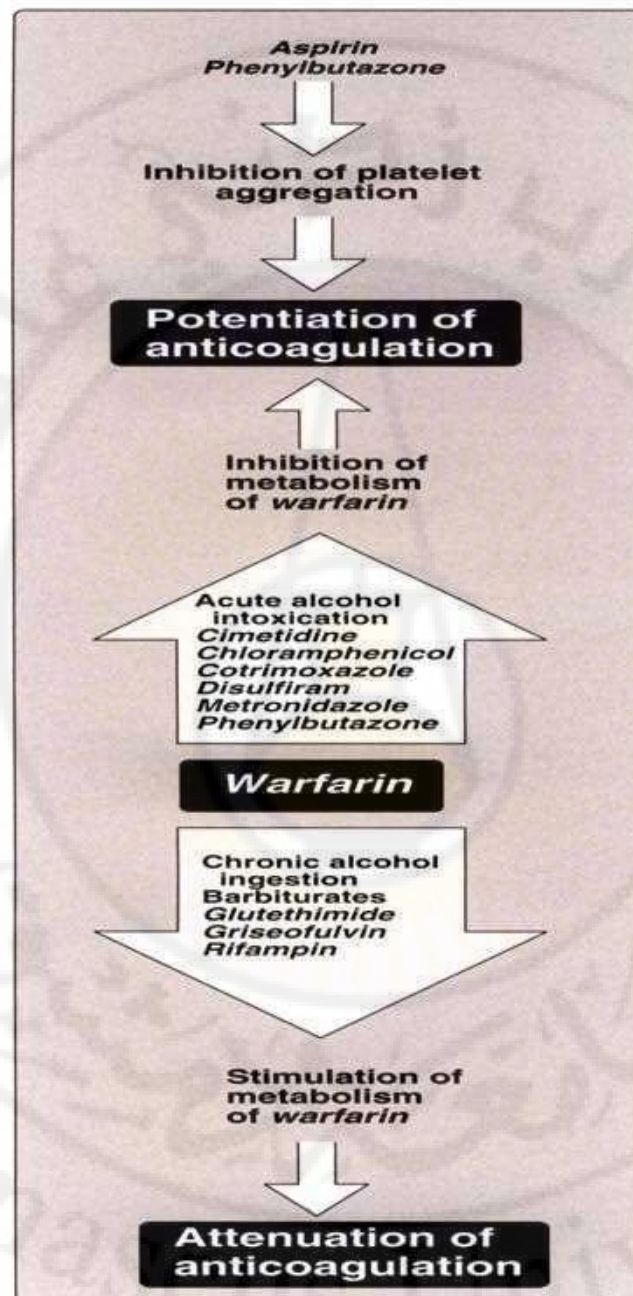


Figure 20.20
Drugs affecting the anticoagulant effect of warfarin.



❖ Heparin

❑ **A: Parenteral IV or SC.**

Mechanism of action

Heparin

- ✓ **Complexes with antithrombin III.**
- ✓ **Irreversibly in activate the coagulation factors thrombin and factor Xa.**

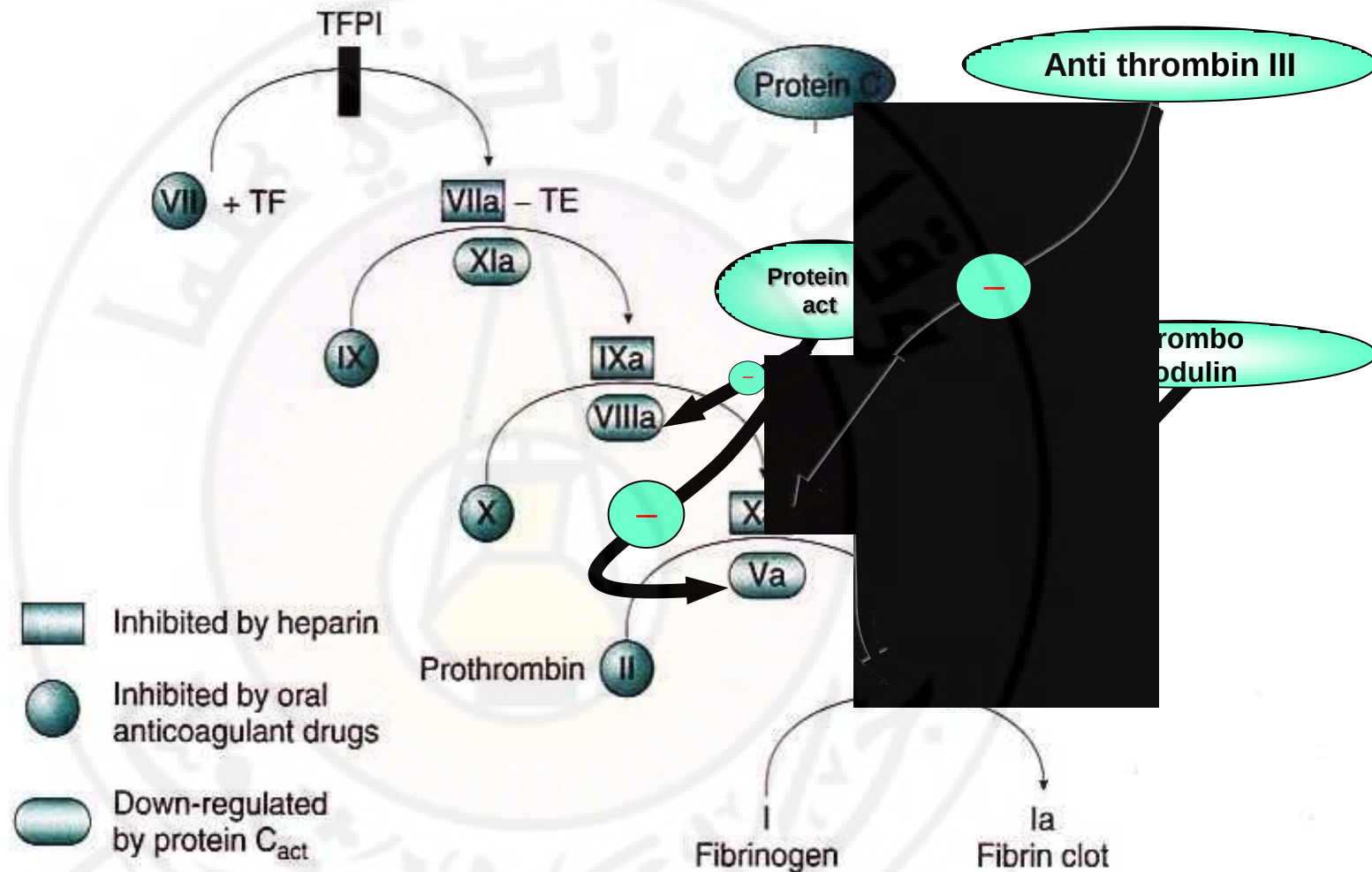


Figure 34-1. A model of the coagulation cascade, including its inhibition by the activated form of the protein C. Tissue factor (TF) is important in initiating the cascade. Tissue factor pathway inhibitor (TFPI) inhibits the action of the VIIa-TF complex. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

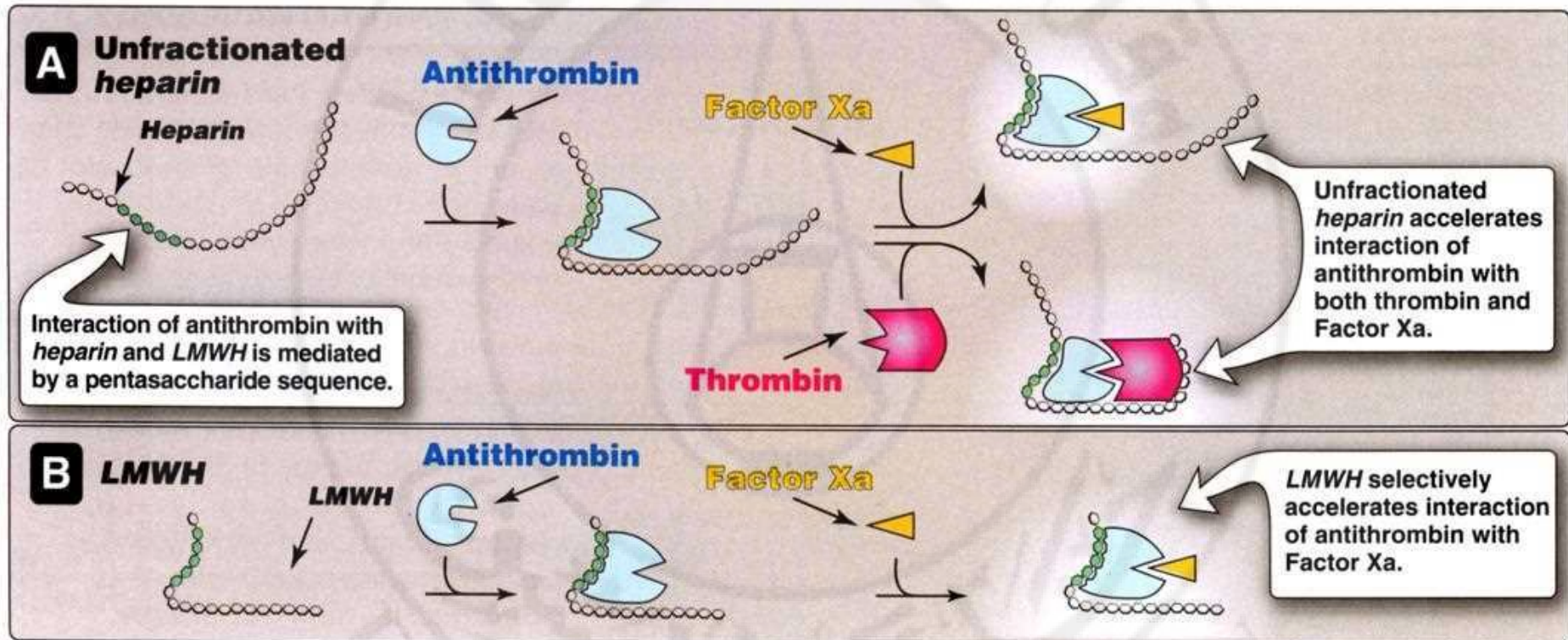


Figure 20.14

Heparin- and low-molecular-weight heparin (LMWH)-mediated inactivation of thrombin or Factor Xa.



Clinical Uses

Heparin

- ❑ Venous thromboses.
- ❑ Pulmonary embolism.
- ❑ Myocardial Infarction.
- ❑ Unstable Angina.
- ❑ Adjuvant to thrombolytics.

Side effects

Heparin

- ❖ Bleeding.
- ❖ Thrombocytopenia.
- ❖ Osteoporosis with chronic use.
- ❖ Protamine is reversal agent.

LMW-Heparins



- ➔ More selective anti-factor X activity.
- ➔ More reliable pharmacokinetics with renal elimination.
- ➔ Less risk of thrombocytopenia.



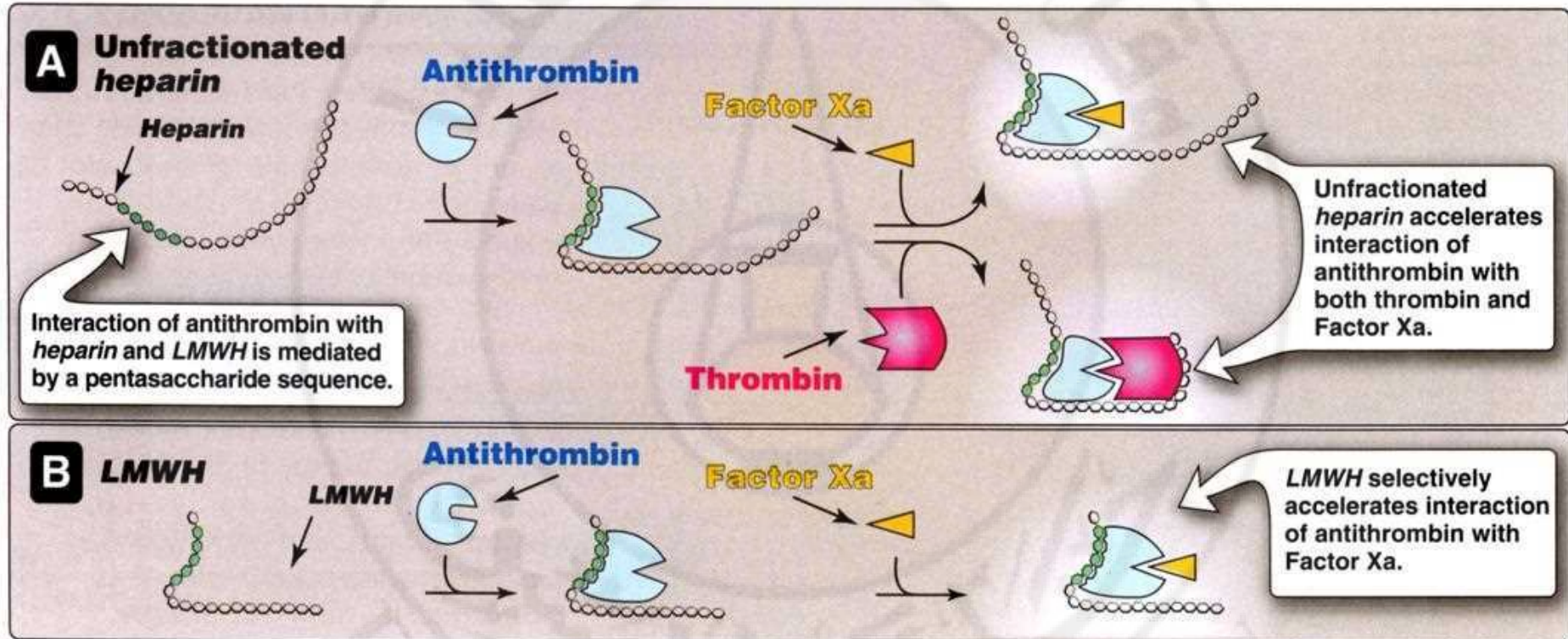


Figure 20.14

Heparin- and low-molecular-weight heparin (LMWH)-mediated inactivation of thrombin or Factor Xa.

Table 34-1. Properties of heparins and warfarin.

Property	Heparins	Warfarin
Structure	Large polymers, acidic	Small lipid-soluble molecule
Route of administration	Parenteral	Oral
Site of action	Blood	Liver
Onset of action	Rapid (seconds)	Slow, limited by half-lives of factors being replaced
Mechanism of action	Activates antithrombin III, which proteolyzes factors including thrombin and factor Xa	Impairs posttranslational modification of factors II, VII, IX, X
Monitoring	aPTT for unfractionated heparin but not LMW heparins	PT
Antidote	Protamine for unfractionated heparin but not LMW heparins	Vitamin K, plasma
Use	Mostly acute, over days	Chronic, over weeks to months
Use in pregnancy	Yes	No



❖ Lepirudin

❏ **A: IV.**

❏ **Direct Thrombin Inhibitor.**

Mechanism of action

Lepirudin

❖ **Binds to thrombin's active site and inhibit its enzymatic action.**



Clinical Uses

Lepirudin

- ❑ In patients with heparin-induced thrombocytopenia (HIT).

Side effects

Lepirudi
II

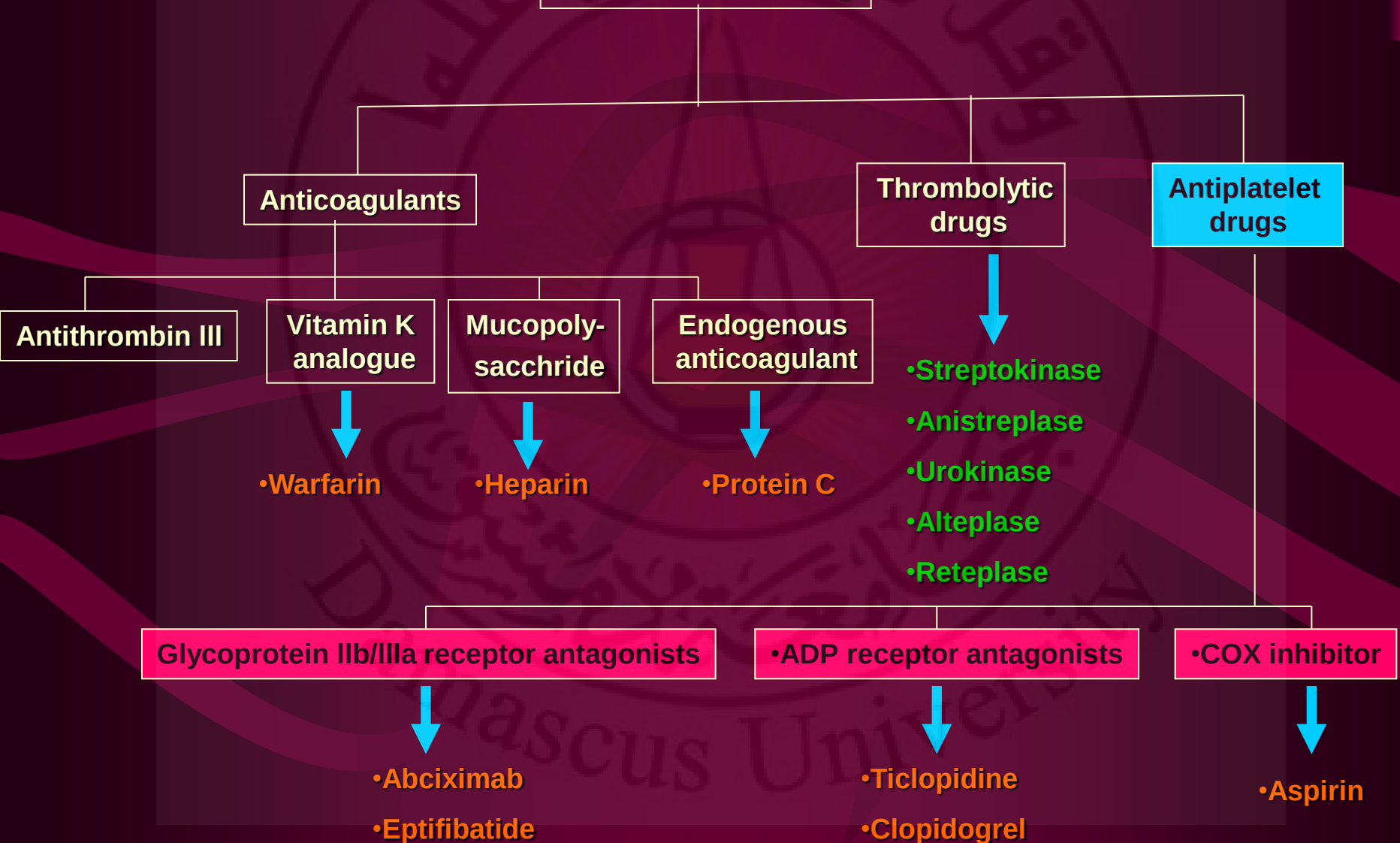
- ❖ Bleeding.
- ❖ Anaphylactic reaction.
- ❖ No reversal agent.
- ❖ Prolonged uses of lepirudin can induce formation of antibodies that form complex with lepirudin and prolong its action.

B. *Reduced anticoagulant action*

1. Barbiturates and other hypnotics (but not benzodiazepines), rifampin and griseofulvin induce the metabolism of oral anticoagulants. The dose of anticoagulant determined during therapy with these drugs would be higher: if the same is continued after withdrawing the inducer—marked hypoprothrombinemia can occur—fatal bleeding is on record.
2. Oral contraceptives: increase blood levels of clotting factors.

Drugs used in clotting disorders

To reduce clotting



A. CLASSIFICATION AND PROTOTYPES

Antiplatelet drugs include **aspirin** and other NSAIDs, glycoprotein IIb/IIIa receptor inhibitors (**abciximab**, **tirofiban**, and **eptifibatide**), antagonists of ADP receptors (**clopidogrel** and **ticlopidine**), and inhibitors of phosphodiesterase 3 (**dipyridamole** and **cilostazol**) (Figure 34–3).



❖ Aspirin

- ❑ **A:** PO.
- ❑ **M:** Extensive first- pass hepatic metabolism.
- ❑ **E:** Metabolites excreted in urine.

Mechanism of action

Aspirin

❖ **Prevents activation of thromboxane A_2
(a potent stimulator of platelet aggregation)
by irreversibly binding to COX.**

Side effects

Aspirin

- ❖ Excessive bleeding.
- ❖ GI bleeding.
- ❖ PUD.



❖ Ticlopidine

- ❑ **A: PO; well absorbed.**
- ❑ **M: Hepatic metabolism.**
- ❑ **E: Metabolites excreted in urine and feces.**



❖ Clopidogrel

❑ **A: PO.**

❑ **M: Hepatic metabolism to active metabolites.**

❑ **E: Metabolites excreted in urine and feces.**

Mechanism of action

Ticlopidine & Clopidogrel

❖ **Irreversible inhibition of ADP- mediated platelet aggregation.**

Side effects

Ticlopidine

- ❖ Excessive bleeding.
- ❖ Nausea.
- ❖ Dyspepsia.
- ❖ Diarrhea.
- ❖ Sever neutropenia (rare).
- ❖ Thrombotic thrombocytopenic purpura.

Side effects

Clopidogrel

- ❖ Fewer side effects than Ticlopidine
- ❖ Thrombotic thrombocytopenic purpura.



❖ Abciximab

❏ **A: IV.**

❏ **E: Rapidly cleared from blood**

(likely secondary to rapid receptor binding).

Mechanism of action

Abciximab

✓ **Human monoclonal antibody directed against the glycoprotein IIb/ IIIa complex..**



❖ Eptifibatide

❏ **A: IV.**

❏ **E: Parent drug and products of its breakdown excreted in urine.**

Mechanism of action

Eptifibatide

✦ **Reversible blockade of glycoprotein IIb/ IIIa receptor..**

Side effects

Abciximab & Eptifibatide

- ❖ Excessive bleeding.
- ❖ Thrombocytopenia with LTU.

Dipyridamole and the newer cilostazol appear to have a dual mechanism of action. They prolong the platelet-inhibiting action of intracellular cAMP by inhibiting phosphodiesterase 3, an enzyme that degrades cAMP. They also inhibit the uptake of adenosine by endothelial cells and erythrocytes and thereby increase the plasma concentration of adenosine. Adenosine acts through platelet adenosine A_2 receptors to increase platelet cAMP and inhibit aggregation.

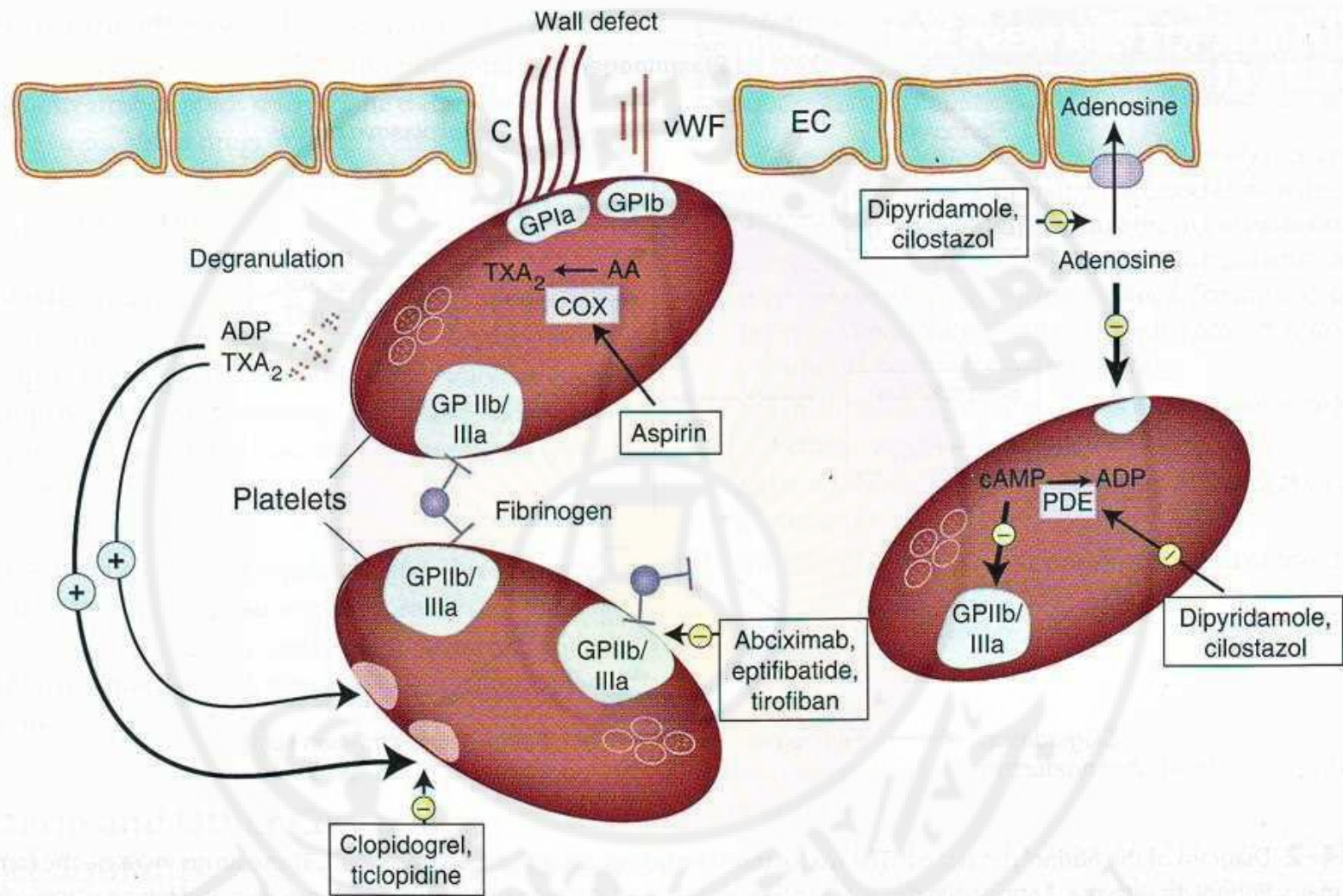


FIGURE 34–3 Thrombus formation at the site of the damaged vascular wall (EC, endothelial cell) and the role of platelets and clotting factors. Platelet membrane receptors include the glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and GP IIb/IIIa, which binds fibrinogen and other macromolecules. Antiplatelet prostacyclin (PGI₂) is released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A₂ (TXA₂), and serotonin (5-HT). (Modified and reproduced, with permission, from Katzung BG, Masters SB, and Trevor AT editors: *Basic & Clinical Pharmacology*, 11th ed. McGraw-Hill, 2009: Fig. 34–1.)

thrombosis

Ticlopidine: Older ADP receptor antagonist with more toxicity, particularly leukopenia and thrombotic thrombocytopenic purpura

Dipyridamole

Dipyridamole

Inhibits adenosine uptake and inhibits phosphodiesterase enzymes that degrade cyclic nucleotides (cAMP, cGMP)

Prevention of thromboembolic complications of cardiac valve replacement; combined with aspirin for secondary prevention of ischemic stroke

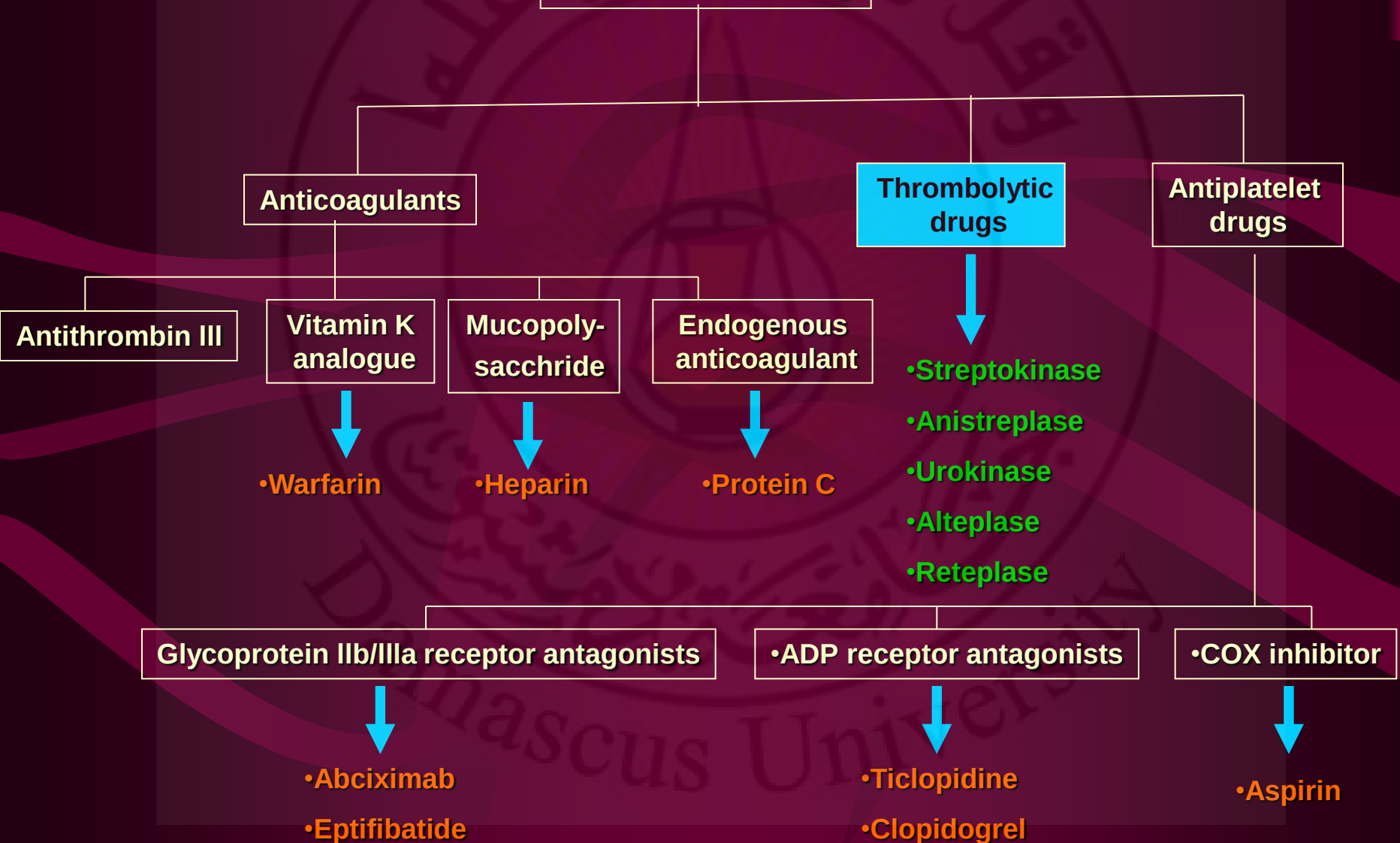
Oral administration

Headache, palpitations, contraindicated in congestive heart failure

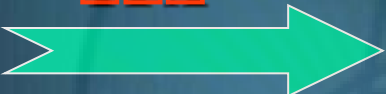
Damascus University

Drugs used in clotting disorders

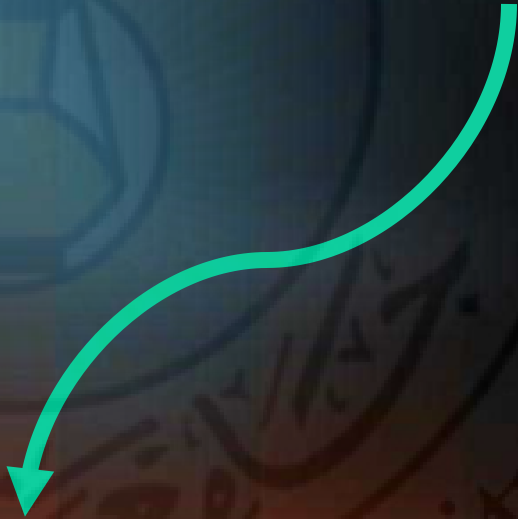
To reduce clotting



Thrombolytic Agents

Plasminogen  *Plasmin*  *Fibrin*

Fibrinolysis



Pharmacokinetics

Streptokinase

❑ **A: IV.**

❑ **M: Cleared from blood by antibodies and reticuloendothelial system.**

Mechanism of action

Streptokinase

- Protein from *Streptococcus* that converts plasminogen to plasmin.
- Plasmin then functions to break up the clot by dissolving fibrin.

Side effects



- ➔ **Excessive bleeding.**
- ➔ **Cerebral hemorrhage.**
- ➔ **Fever, allergic reactions, and therapeutic resistance in patients with streptococcal antibodies.**

Pharmacokinetics

Anistreplase

❏ **A: IV.**

❏ **M: Breaks down into components following administration.**

Mechanism of action

Anistreplase

- Human plasminogen and bacterial streptokinase that has been acylated to protect the enzyme' active site.

Side effects



- ➔ **Excessive bleeding.**
- ➔ **Cerebral hemorrhage.**

Pharmacokinetics

Urokinase

- ❑ **A: IV.**
- ❑ **M: Rapidly cleared from blood.**
- ❑ **E: Small amount excreted in urine and feces.**

Mechanism of action

Urokinase

- Human enzyme produced by the kidney that converts plasminogen to plasmin.
- Plasmin then functions to break up the clot by dissolving fibrin.

Pharmacokinetics

Alteplase

- ❑ **A: IV.**
- ❑ **M: Principally cleared by liver.**
- ❑ **E: In urine.**

Pharmacokinetics

Reteplase

❏ **A: IV.**

❏ **E: Cleared by kidneys and liver.**

Mechanism of action

Reteplase

- Human t- PA from which several amino acids have been deleted..
- Converts fibrin- bound plasminogen to plasmin (clot selective).

Patients with chronic atrial fibrillation, a common supraventricular arrhythmia, routinely receive warfarin to prevent the formation of blood clots in the poorly contracting atrium and to decrease the risk of embolism of such clots to the brain or other tissues. Such patients are also often treated with antiarrhythmic drugs. The primary goals of antiarrhythmic treatment are to slow the atrial rate and, most importantly, control the ventricular rate.

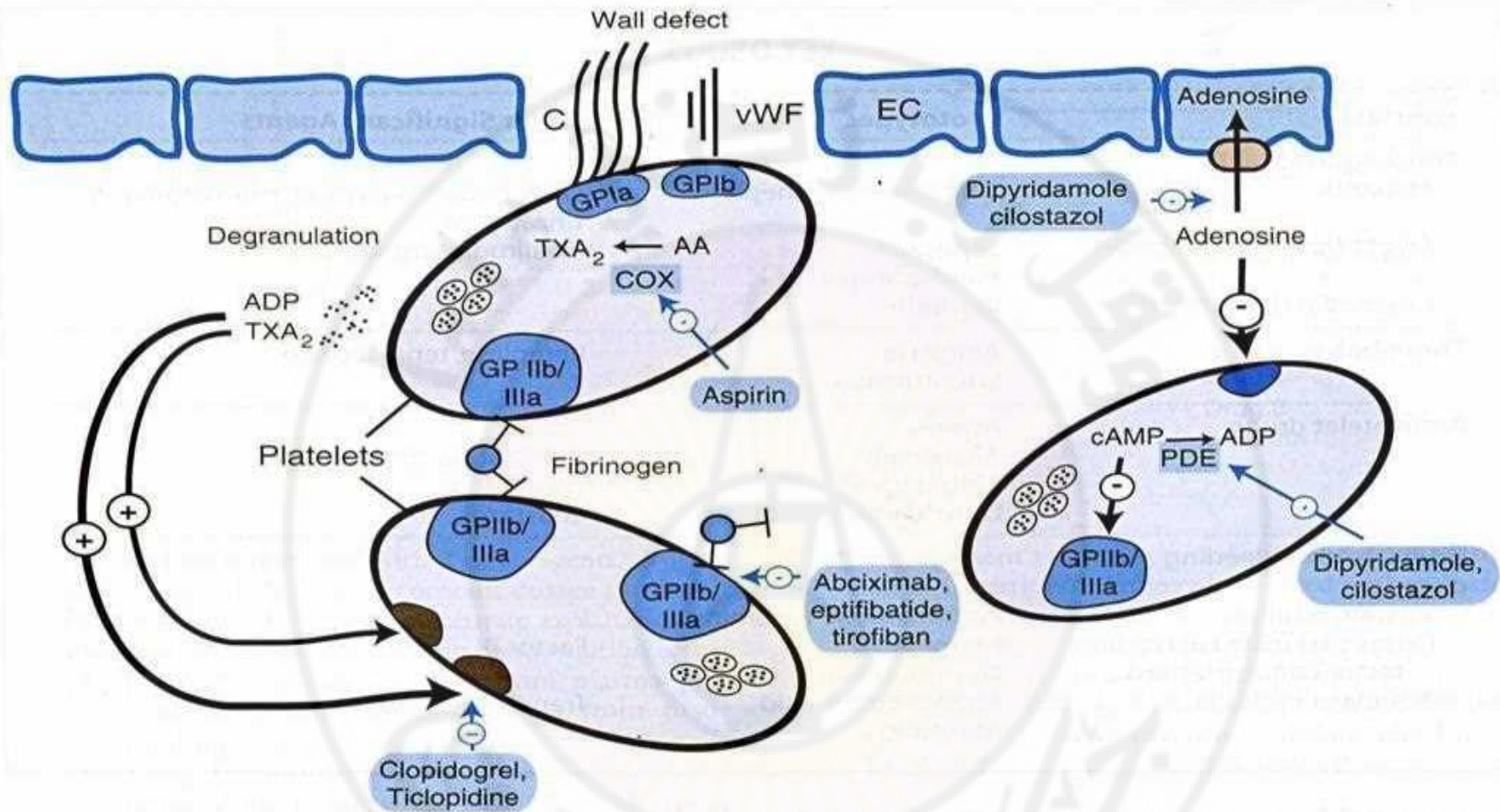


Figure 34–3. Antiplatelet drug mechanisms. At the site of blood vessel wall defects and damage endothelial cells (EC), the exposure of collagen (C) and von Willebrand factor (vWF) activates platelets by binding to platelet membrane glycoproteins (GP) 1a and 1b. Platelet activation triggers degranulation and the release of adenosine diphosphate (ADP) and thromboxane A₂ (TXA₂), which act through platelet receptors to modify GPIIb/IIIa so it is able to bind fibrinogen and cross-link platelets. Aspirin inhibits the production of TXA₂ by irreversibly inhibiting cyclooxygenase (COX). Abciximab, eptifibatide, and tirofiban inhibit the binding of GPIIb/IIIa to fibrinogen, while clopidogrel and ticlopidine irreversibly inhibit the ADP receptor. Dipyridamole and cilostazol inhibit GPIIb/IIIa activation by inhibiting the phosphodiesterase enzyme (PDE) that degrades cAMP and by inhibiting the uptake by EC of adenosine, an endogenous inhibitor of platelet function. (Redrawn and reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 10th ed. McGraw-Hill, 2007.)

I, II, III, IV

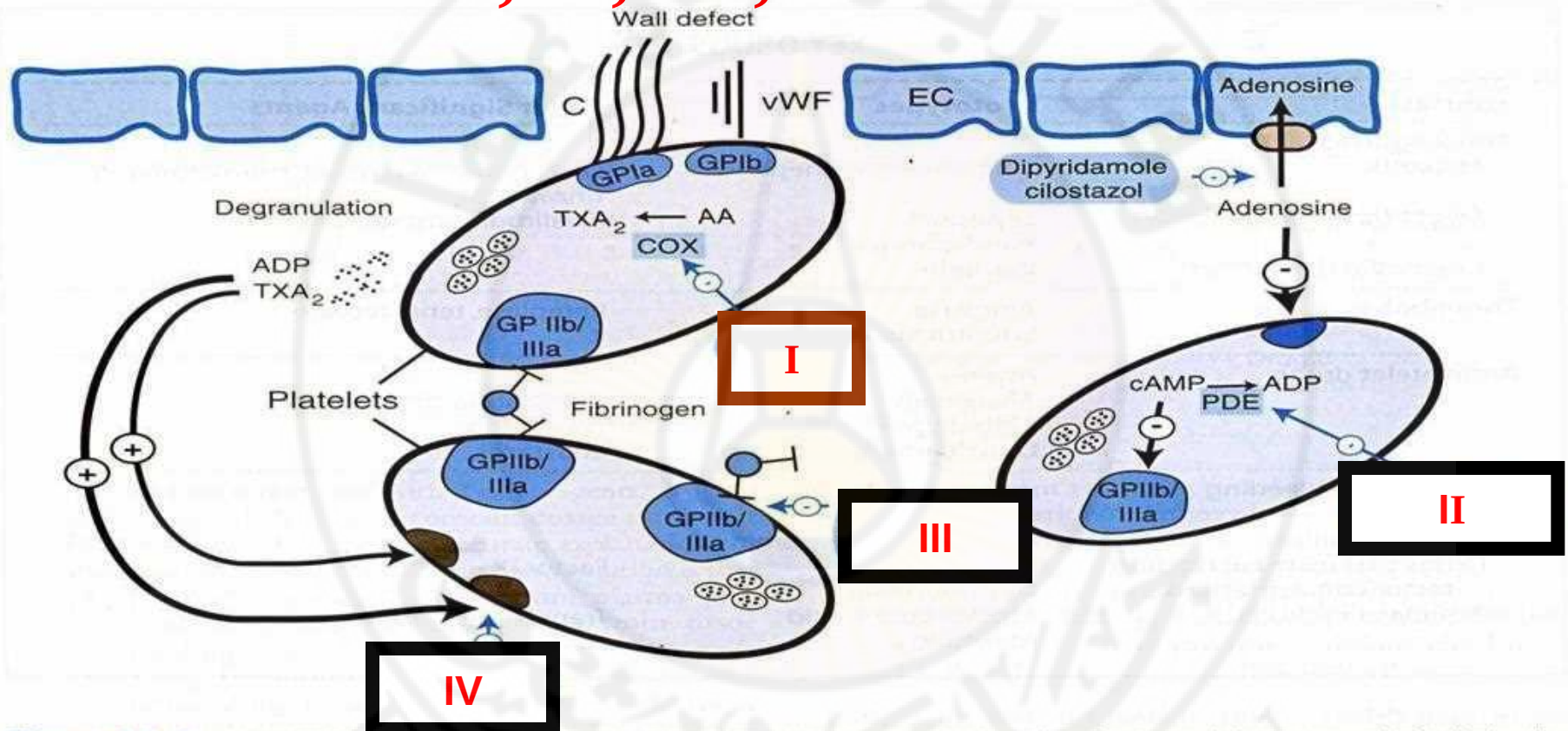


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To facilitate clotting

***Antiplasmin
drugs***

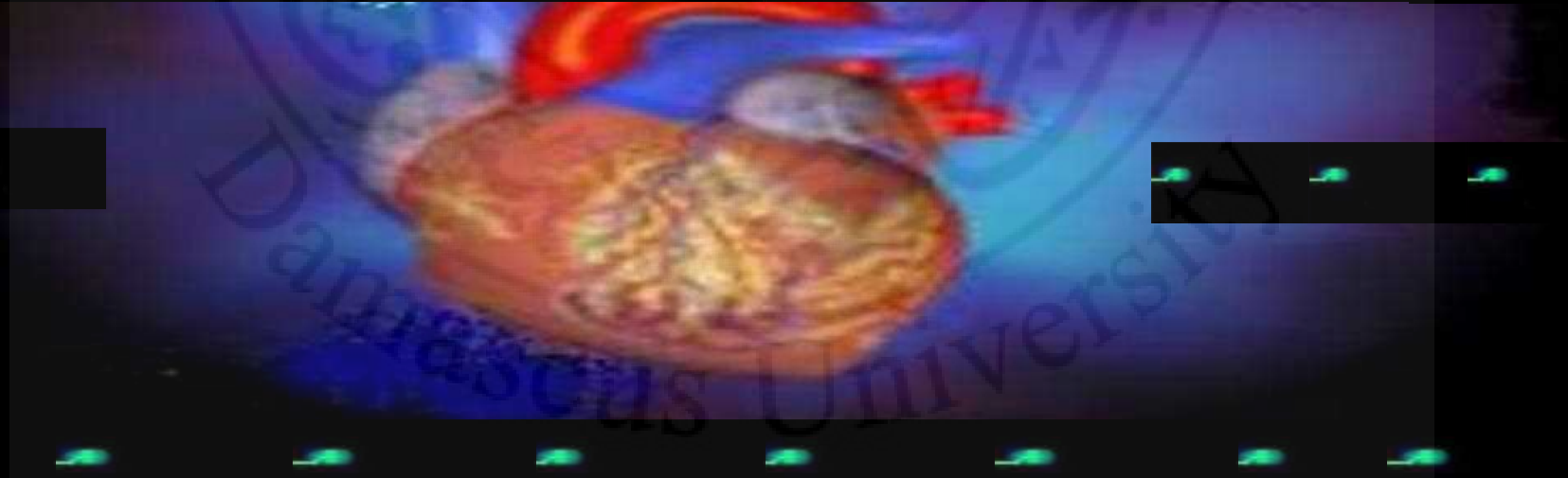
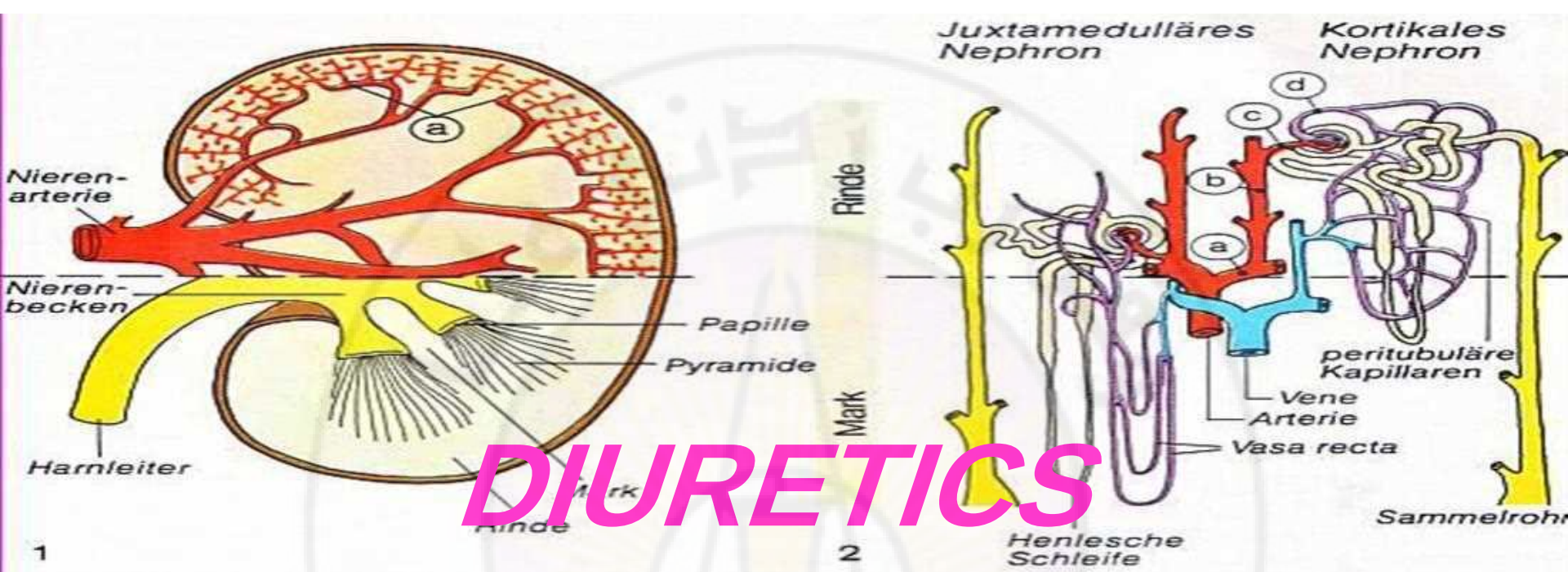
***Clotting
factors***

***Vitamin
K***

- **Aminocaproic acid**

شكراً على الإصغاء

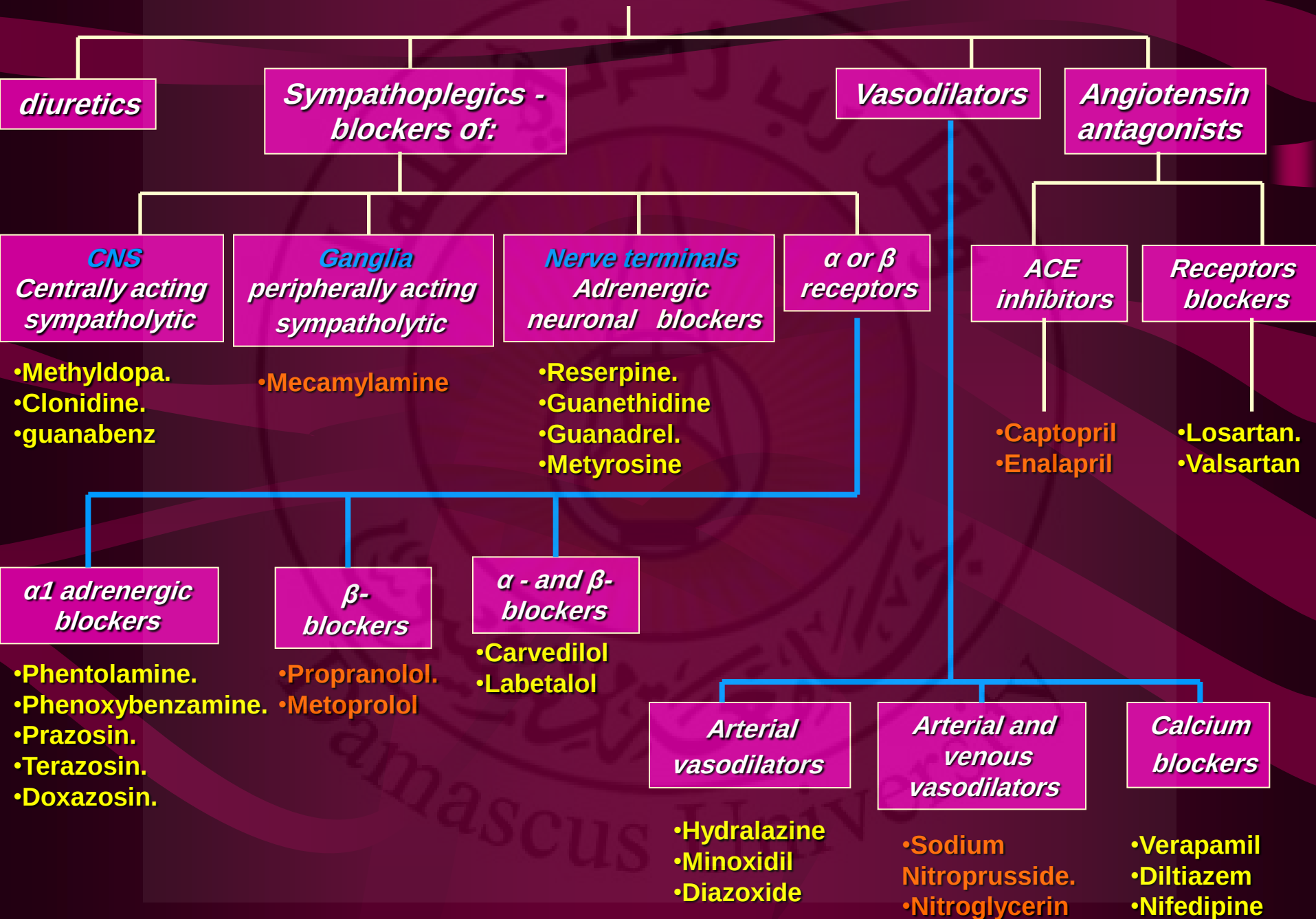
شكراً على الإصغاء





Antihypertensive Drugs

Antihypertensive drugs by class



I. OVERVIEW

Drugs inducing a state of increased urine flow are called diuretics. These agents are inhibitors of renal ion transporters that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ and other ions, such as Cl^- , enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium. Diuretics thus increase the volume of both urine, and often change its pH as well as the ionic composition of the urine and blood. The efficacy of the different classes of diuretics varies considerably, with the increase in Na^+ secretion varying from less than two percent for the weak, potassium-sparing diuretics to over twenty percent for the potent loop diuretics. In addition to these ion-transport inhibitors, there are osmotic diuretics that prevent water reabsorption, as well as aldosterone antagonists, and a carbonic anhydrase inhibitor. The major clinical uses of diuretics are in managing disorders involving abnormal fluid retention (edema) or treating hypertension in which their

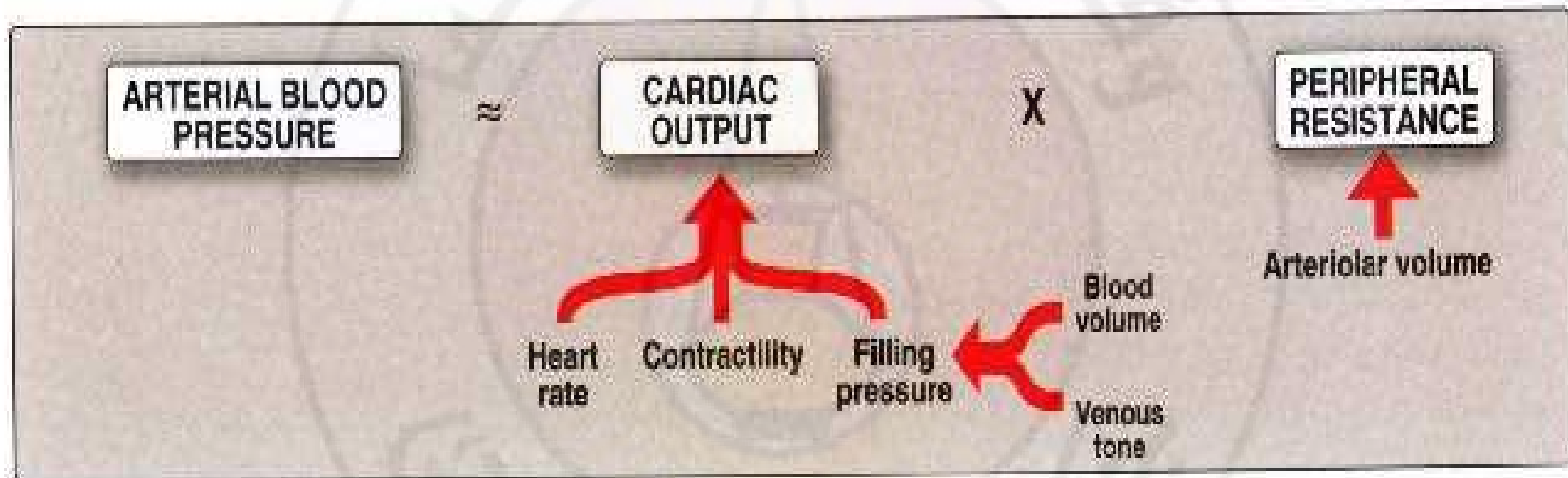


Figure 19.2

Major factors influencing blood pressure.

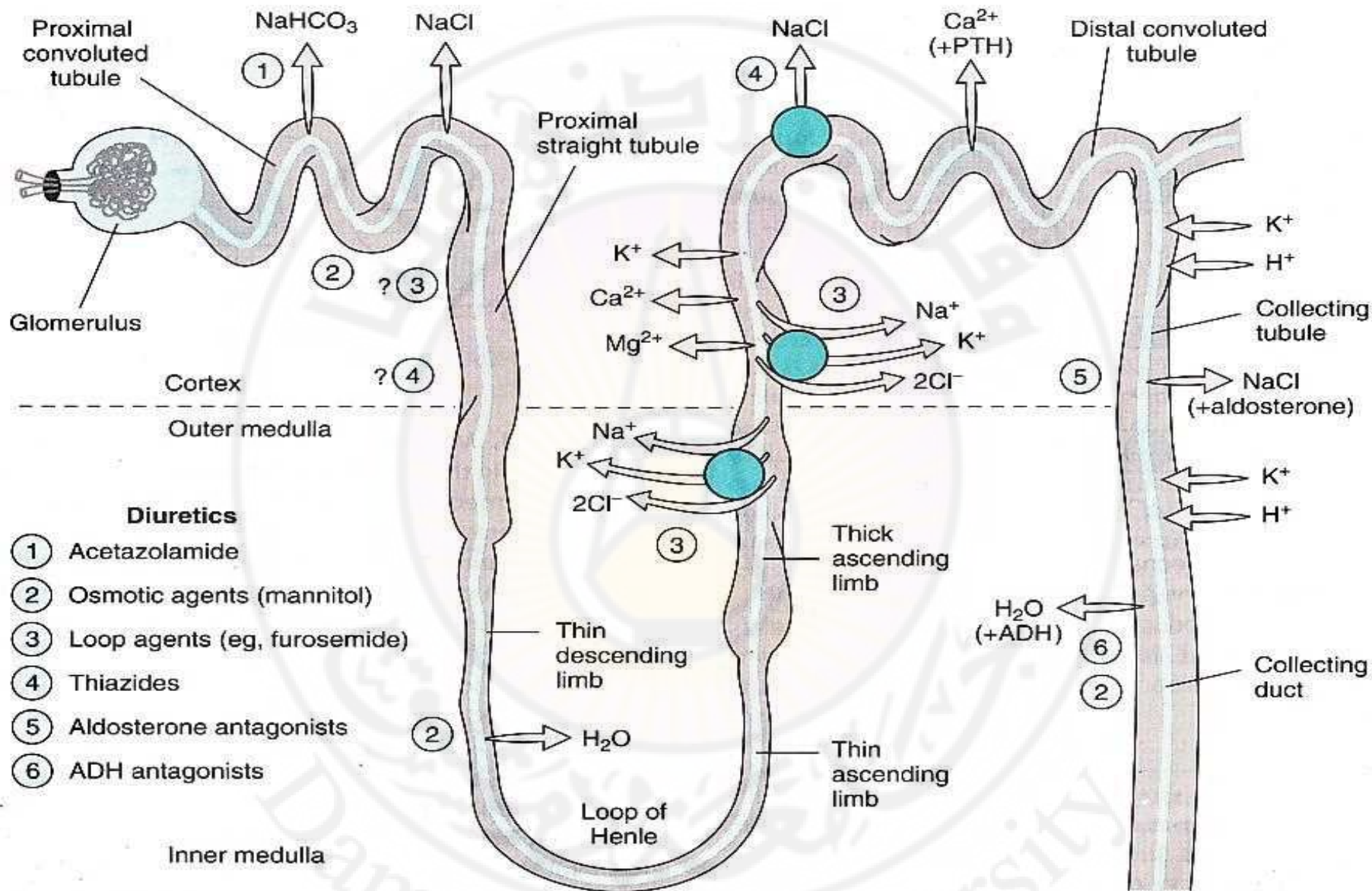


Figure 15–1. Tubule transport systems and sites of action of diuretics. Circles with arrows denote known ion cotransporters that are targets of the diuretics indicated by the numerals. Question marks denote preliminary or incompletely documented suggestions for the location of certain drug effects. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

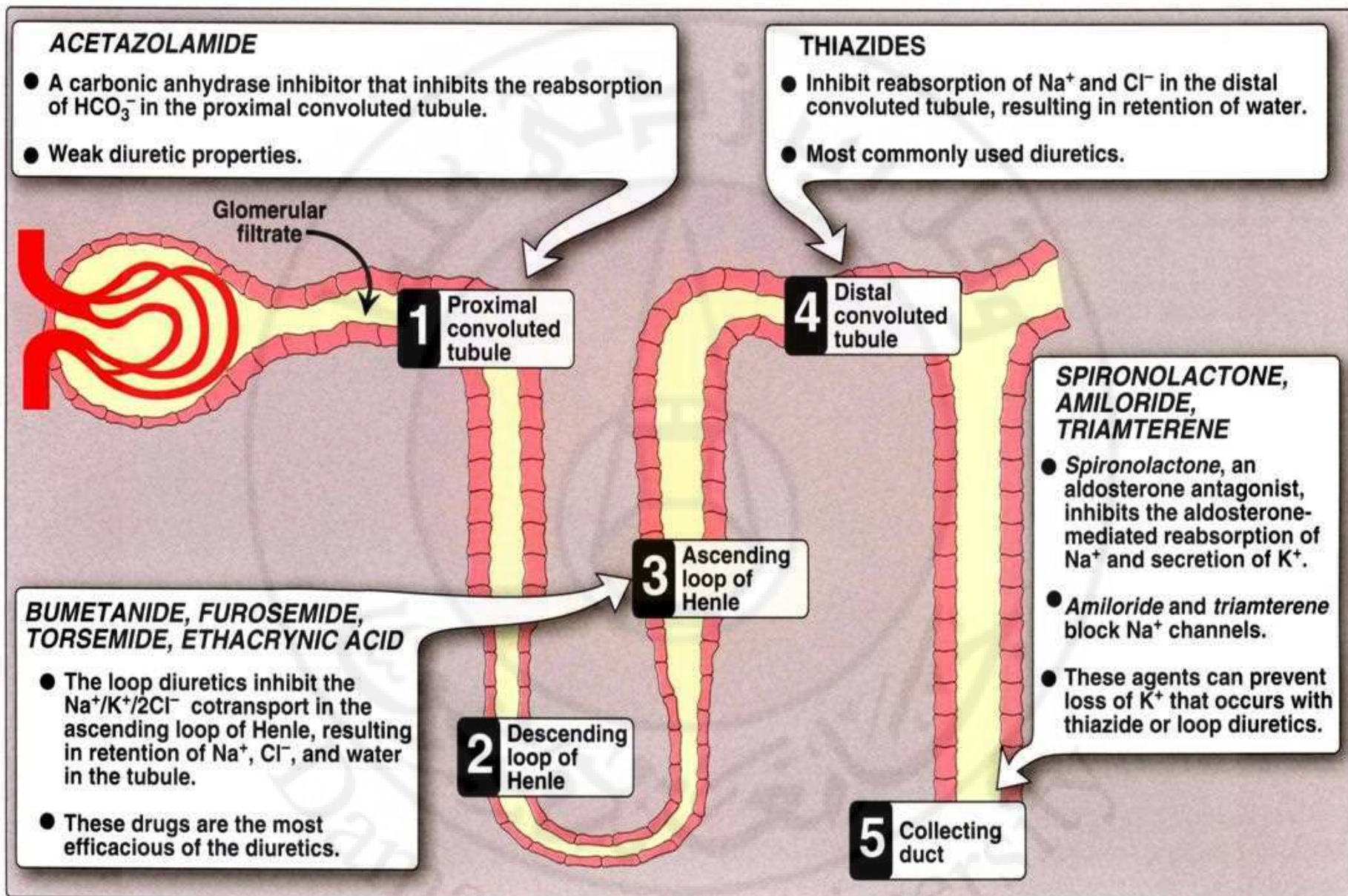
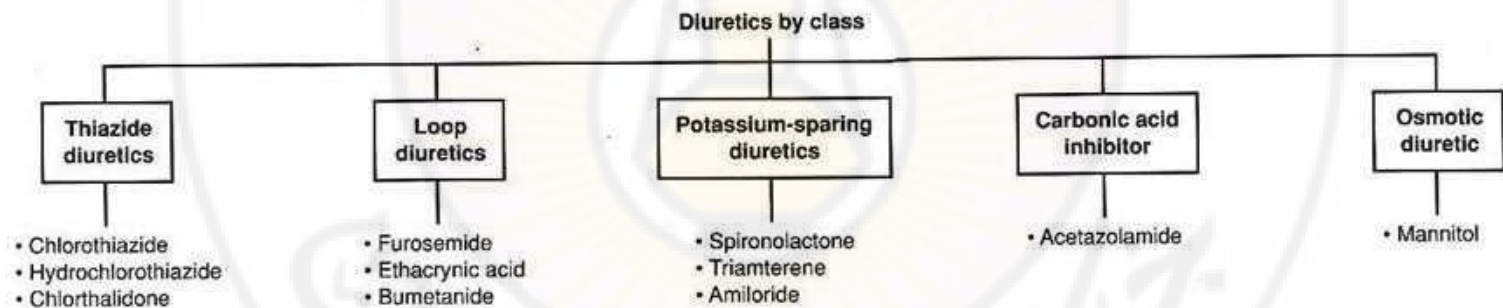


Figure 22.2

Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

CLASSIFICATION OF DIURETICS



CARBONIC ACID INHIBITOR AND OSMOTIC DIURETICS

Drug

Carbonic Acid Inhibitor (CAI) Diuretics

Acetazolamide



Pharmacokinetics

- ▣ A: PO and IV
- ▣ E: Unchanged in urine
- ▣ Urine chemistry: Increased Na^+ , HCO_3^- , water, pH, K^+ ; decreased Cl^-

Mechanism of Action

Prevents the reabsorption of bicarbonate at the proximal convoluted tubule

Na^+ increases in the urine because H^+ is no longer being excreted to combine with HCO_3^-

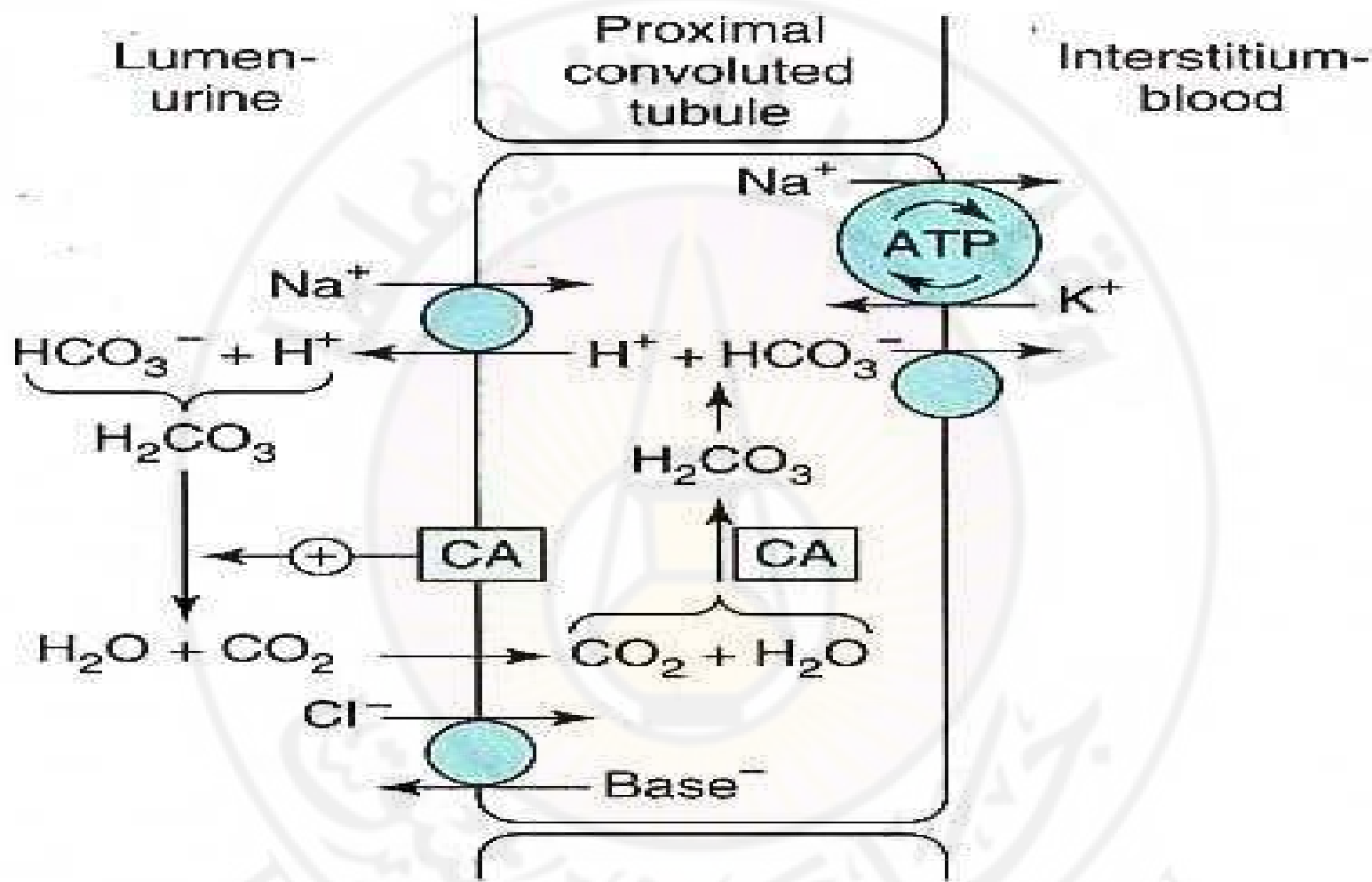


Figure 15–2. Mechanism of sodium bicarbonate reabsorption in the proximal tubule cell. CA, carbonic anhydrase. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

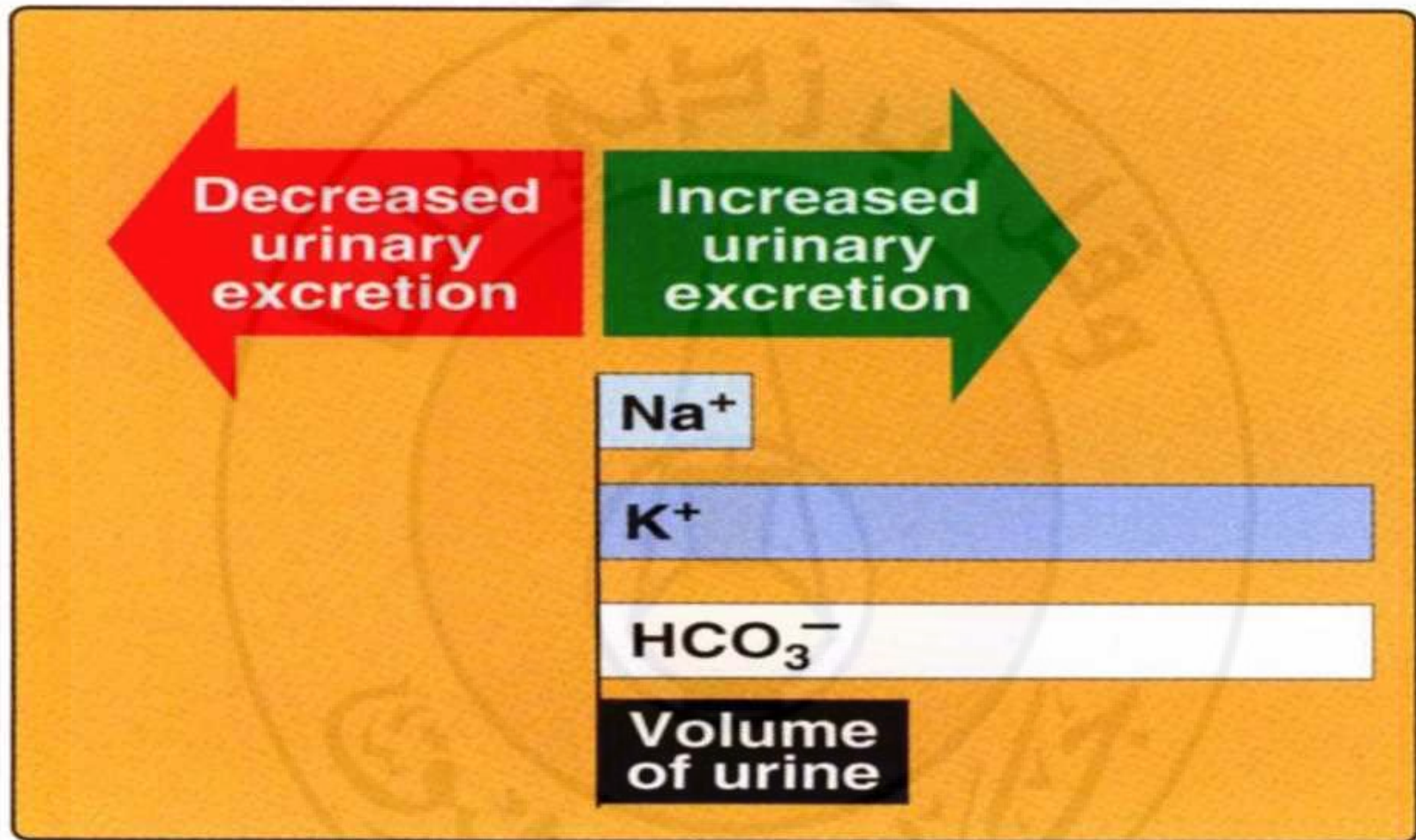


Figure 22.10

Relative changes in the composition of urine induced by *acetazolamide*.

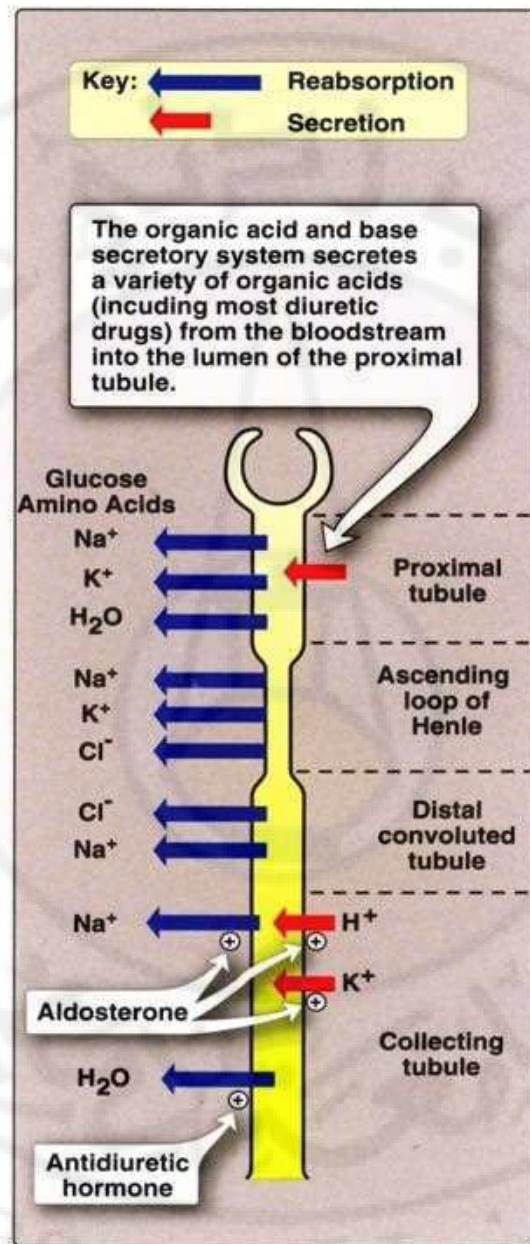


Figure 22.3

Sites of transport of solutes and water along the nephron.

Clinical Uses

Glaucoma (carbonic anhydrase is important in the production of aqueous humor)

Metabolic alkalosis

Altitude sickness

Damascus University

Side Effects

Paresthesias

Tinnitus

GI upset

Hyperchloremic metabolic acidosis

Neuropathy

Ammonia toxicity

Sulfa drug allergy

OSMOTIC DIURETICS

Drug

Osmotic Diuretics

Mannitol

Damascus University

Pharmacokinetics

A: IV

M: Metabolized to a minor degree in the liver to glycogen

E: Most is excreted unchanged in urine

Mechanism of Action

Raises solutes in the blood causing hypertonic blood, which draws fluid out of the tissues

Increased plasma volume will deliver more volume to the kidney leading to increased GFR, which leads to increased urinary output

Clinical Uses

Reduction of intraocular or intracranial pressure (CNS trauma with swelling and edema)

Maintain urinary output for renal protection (ie, rhabdomyolysis or hemolysis)

Acute altitude sickness → Good for head swelling, bad for heart swelling

Side Effects

Transiently causes increased intravascular pressure,
which can exacerbate CHF or hypertension

Dehydration

Hypernatremia

Damascus University

LOOP Diuretics

Drug

Loop Diuretics

Furosemide

(Lasix)

Damascus University

Pharmacokinetics

A: IV, IM, and PO

DOA: 6-8 hours

M: Metabolized to a small degree in the liver

E: Metabolized and parent drug excreted in urine

Urine chemistry: Increased Na^+ , Cl^- , K^+ , water, Ca^{2+} , Mg^{2+} ; decreased HCO_3^- and pH

Mechanism of Action

Block reabsorption of Na^+ and Cl^- in the cortex and medullary regions of the ascending loop of Henle



Clinical Uses and General Information

Hyperkalemia

Acute hypertension states

Drugs of choice for edematous situations

Acute renal failure

Hypercalcemia

10 time more efficacious than thiazide diuretics

Side Effects

Hyperglycemia: similar effect on pancreas as thiazides

Hyperuricemia

Hypocalcemia or hypercalcemia

Hypokalemia

Hypokalemic metabolic acidosis

Hyponatremia

Ototoxicity (reversible tinnitus)

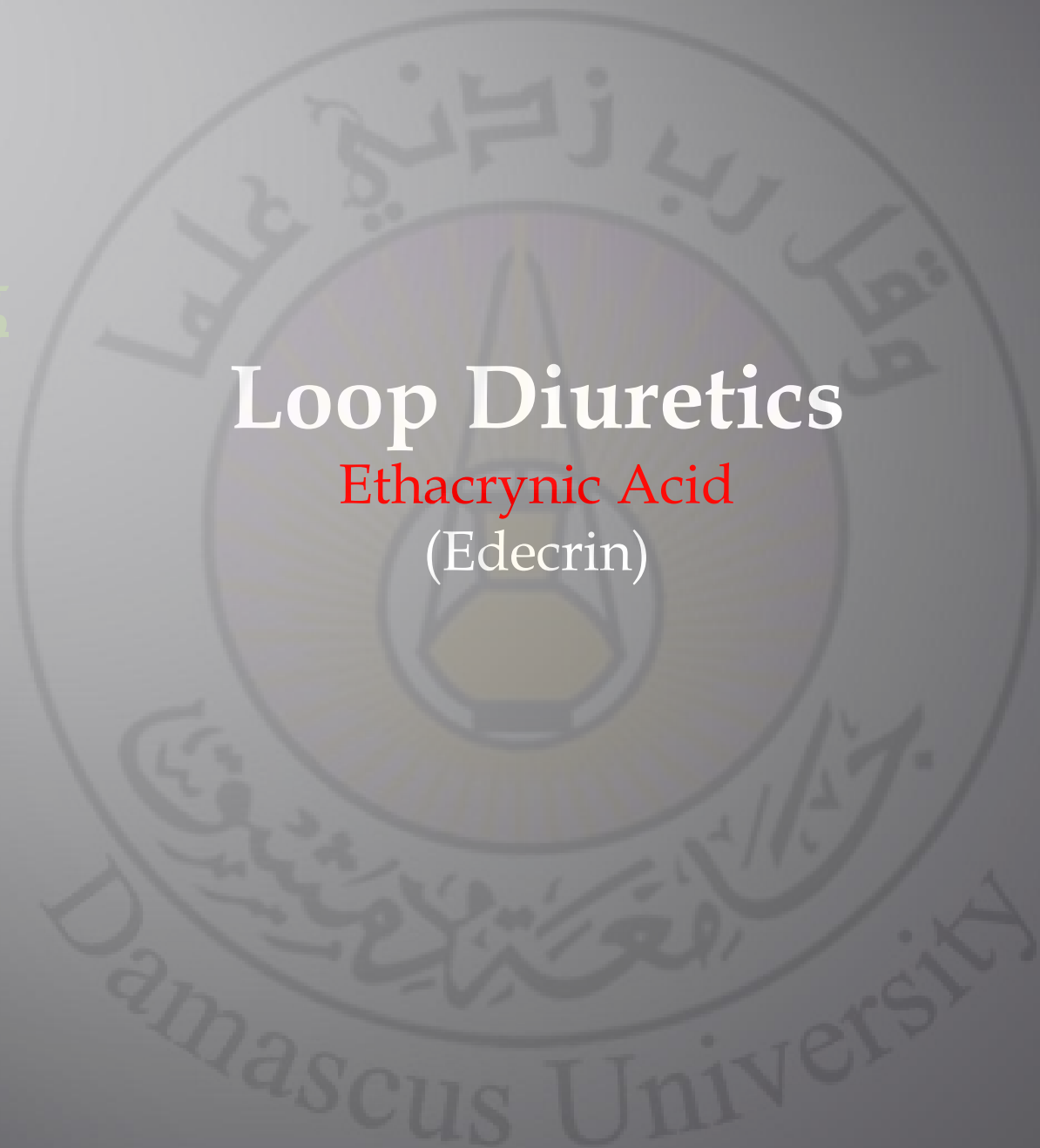
Interstitial nephritis

Drug

Loop Diuretics

Ethacrynic Acid

(Edecrin)



Drug

Loop Diuretics

Bumetanide

(Bumex)



THIAZIDE DIURETICS

Drug

:Thiazide Diuretics

Chlorothiazide (Diuril)

Damascus University

Pharmacokinetics

- ▣ A: PO and IV
- ▣ DOA: 6-12 hours
- ▣ E: Unchanged in urine
- ▣ Urine chemistry (opposite of blood chemistry):
Increased Na^+ , Cl^- , K^+ , water, and Mg^{2+} ;
decreased Ca^{2+} and pH

Mechanism of Action

- ▣ Increase urinary and salt output by inhibiting Na^+ and Cl^- reabsorption in the distal tubule

Clinical Uses and General Information

Hypertension

CHF

Nephrolithiasis due to hypercalciuria

Diabetes insipidus

Damascus University

Side Effects

Hypercalcemia

Hyperglycemia

Hyperlipidemia

Hypomagnesemia

Hyperuricemia (increased risk for gout)

Hypokalemia

Hyponatremia

Metabolic alkalosis

Muscle weakness (due to loss of salt)

Pancreatitis (decreased insulin release)

Vasodilation

Drug:

▣ Thiazide Diuretics

Hydrochlorothiazide
(HydroDIURIL, HCTZ)

Drug

Thiazide Diuretics

Chlorthalidone

(Hygroton)



POTASSIUM-SPARING DIURETICS

Drug

Potassium Sparing Diuretics

Spironolactone
(Aldactone)



Pharmacokinetics

A: PO

M: Metabolized to active metabolites

E: Majority of metabolites excreted in urine;
remaining excreted in feces

Urine chemistry: K^+ is lower than Na^+

Mechanism of Action

Block the effects of aldosterone in the collecting duct leading to Na^+ loss and K^+ retention



Clinical Uses and General Information

Increased aldosterone states (Conn's syndrome, ectopic ACTH production, or secondary hyperaldosteronism due to CHF, nephritic syndrome, or hepatic cirrhosis)

Often combined with thiazides to treat hypertension and prevent hypokalemia

Side Effects

Hyperkalemia (especially with ACE inhibitors, angiotensin receptor blockers, β -blockers, and NSAIDs)

CNS depression causing drowsiness

Metabolic acidosis

Gynecomastia with spironolactone

Nephrolithiasis with triamterene

Drug

Potassium Sparing Diuretics

Triamterene

(Dyrenium)

Pharmacokinetics

A: PO

M: Hepatic metabolites

E: Parent drug and metabolites excreted in urine

Mechanism of Action

Retain K^+ and Na^+ in the collecting duct but does not work on aldosterone



Drug

Potassium Sparing Diuretics

Amiloride

(Midamor)



Pharmacokinetics

A: PO

E: Unchanged in urine and feces



SERUM ELECTROLYTE EFFECTS OF DIURETICS

In general, the opposite findings of serum electrolytes are seen in urine.

Type of Diuretic

Thiazide

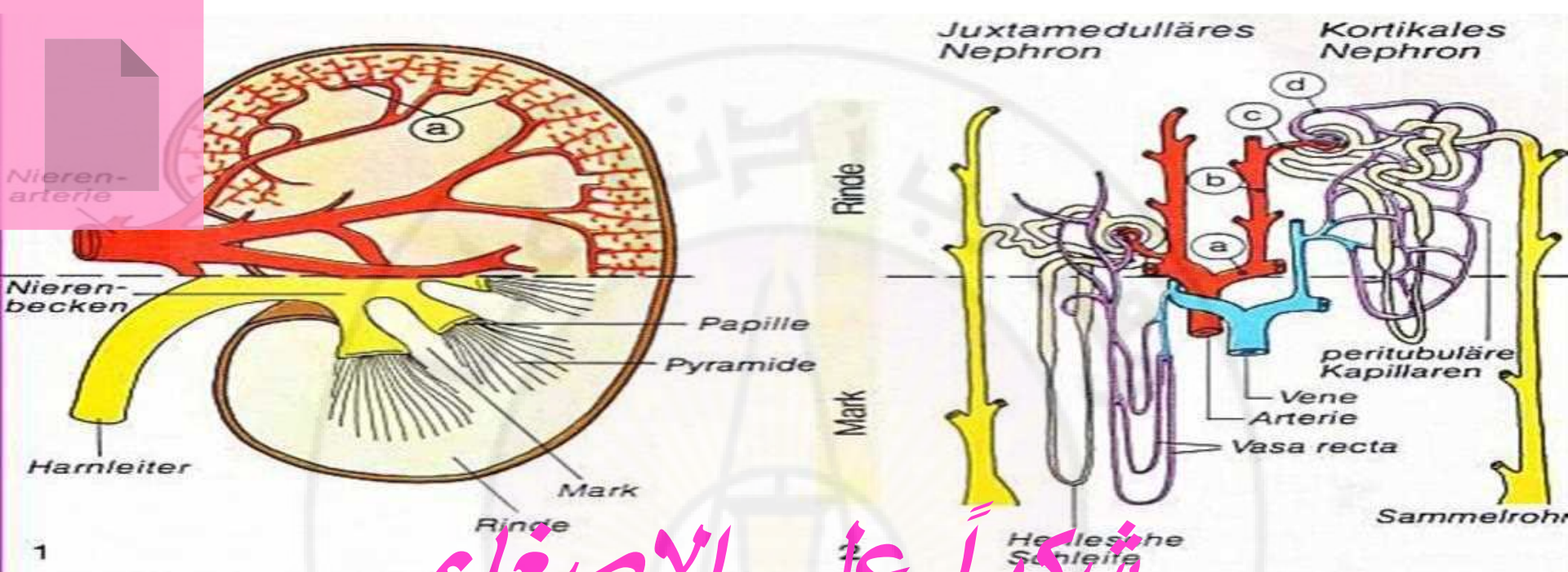
Loop

Potassium-sparing

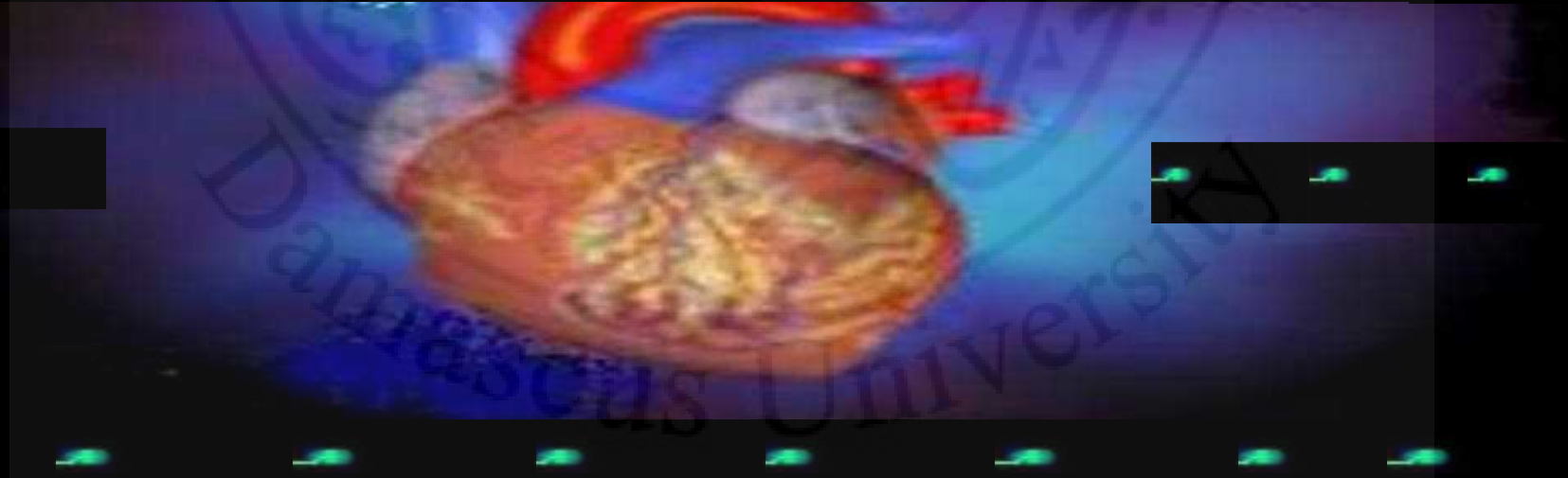
CAI

Damascus University

Type of Diuretic	Ca	Mg	Na	K	AUric acid	Blood Sugar	Lipids	Metabolic Disturbance
Thiazide	↑	↓	↓	↓	↑	↑	↑	Hypokalemic metabolic alkalosis
Loop	↓	↓	↓	↓	↑	↑	-	
Potassium-sparing	-	↑	↓	↑	↑	-	-	Hyperchloremic metabolic acidosis
CAI	-	-	-	↓	↑	↑	-	



نشكراً على الإصغاء



Cardiovascular system



Hypertension



Regular blood pressure tests are important for the early diagnosis of Hypertension.

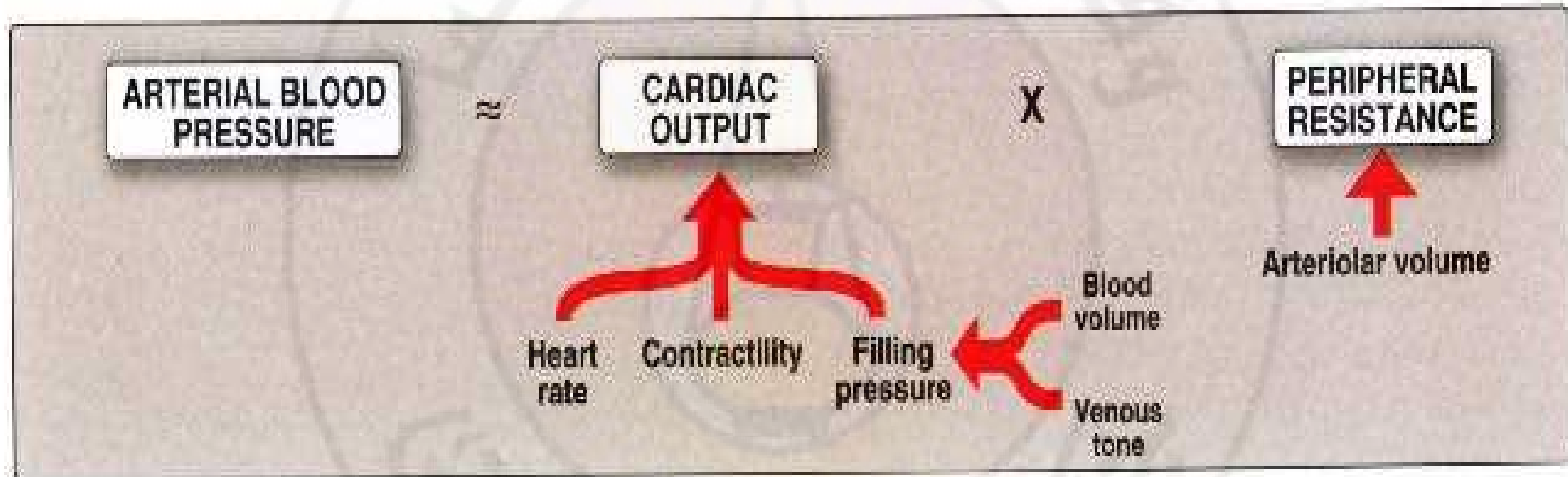


Figure 19.2

Major factors influencing blood pressure.

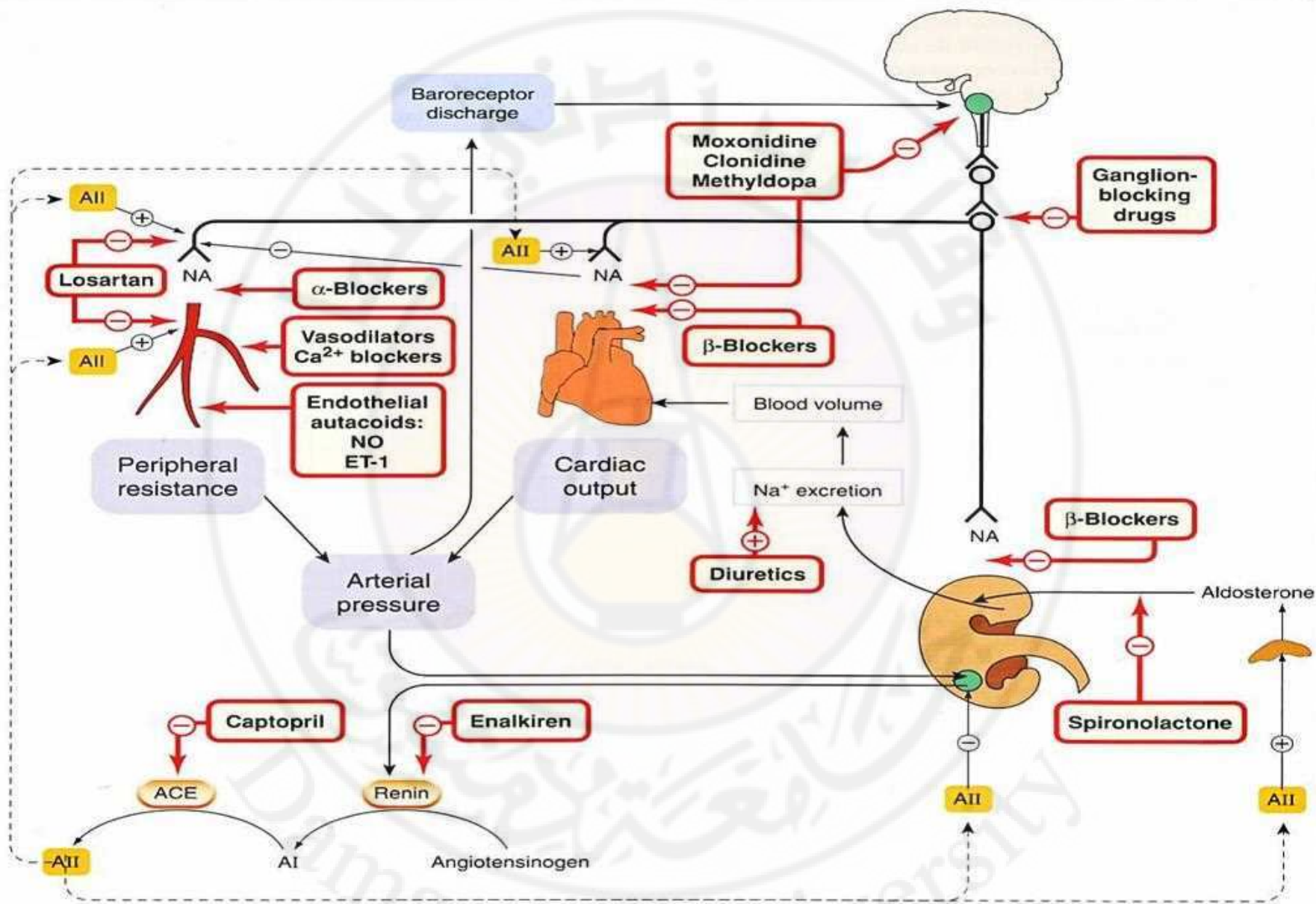
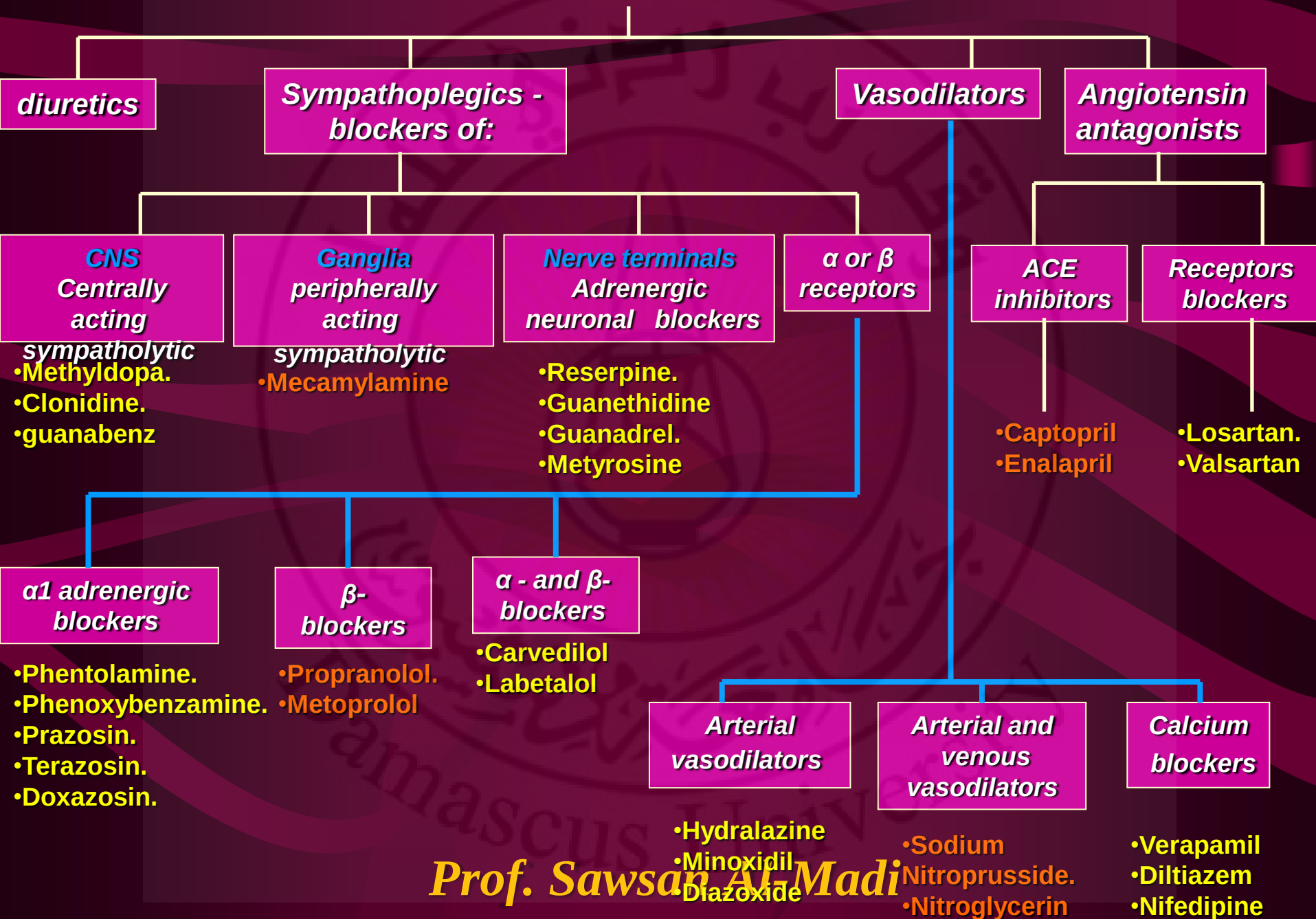


Fig. 18.9 Diagram showing the main mechanisms involved in arterial blood pressure regulation (black lines), and the sites of action of antihypertensive drugs (hatched boxes + orange lines). (NA, noradrenaline; AI, angiotensin I; AII, angiotensin II; ACE, angiotensin-converting enzyme; NO, nitric oxide; ET-1, endothelin-1.)

Antihypertensive Drugs

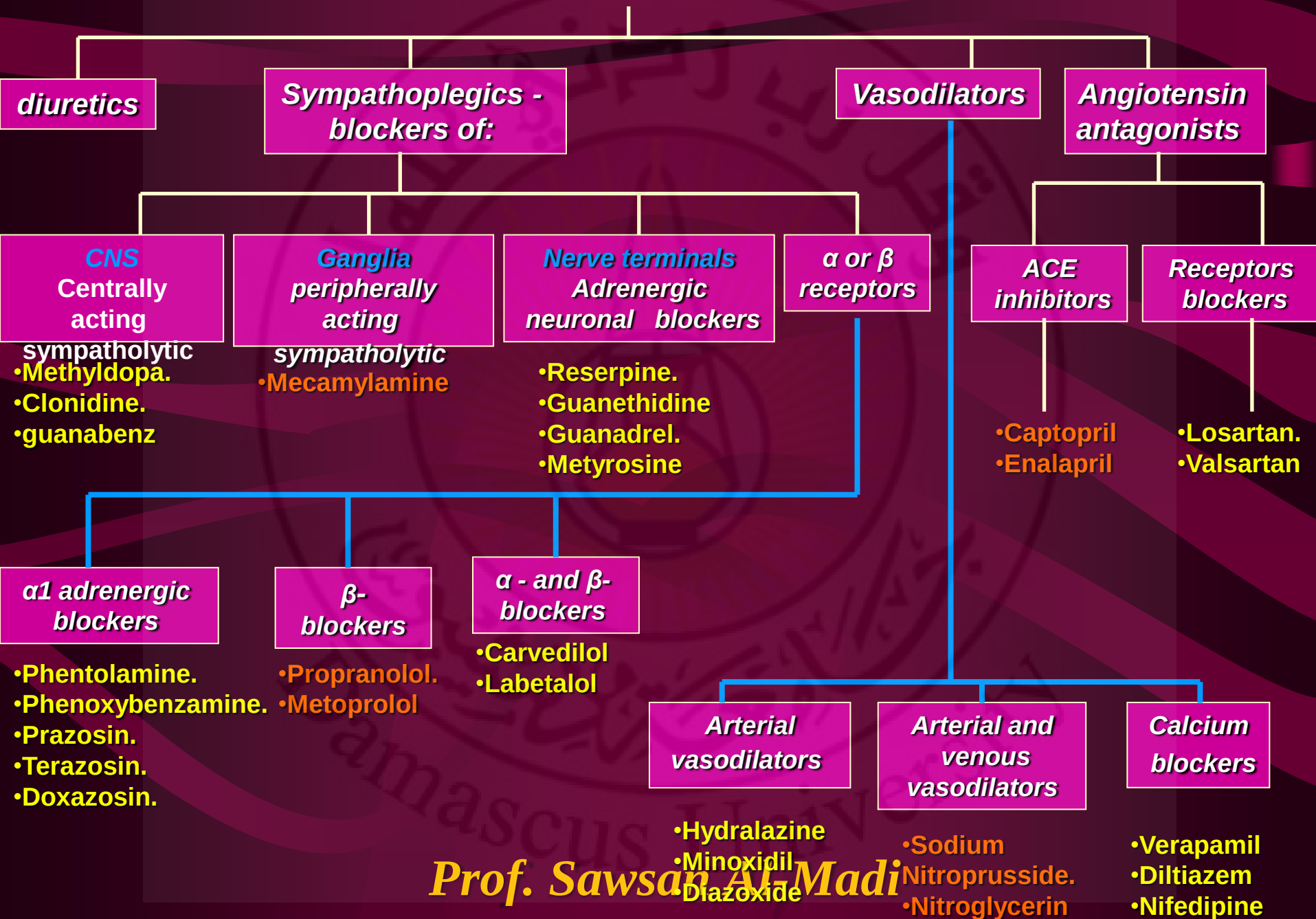
Prof. Sawsan Al-Madi

Antihypertensive drugs by class



Prof. Sawzan Al-Madi

Antihypertensive drugs by class



Prof. Sawzan Al-Madi

Pharmacokinetics

1. Methyldopa (Aldomet)

- **A:** PO and IV.
- **M:** Hepatic metabolism.
- **E:** Parent drug and metabolites excreted in urine.

2. Clonidine (catapres)

- **A:** PO and transdermal patch (good for noncompliant patients; provides steady-state blood levels, also fewer side effects).
- **M:** 50% Hepatic metabolism.
- **E:** Majority excreted unchanged in urine.

3. Guanabenz (Wytensin)

- **A:** PO.
- **M:** Site of metabolism unknown.
- **E:** Metabolites excreted in urine.

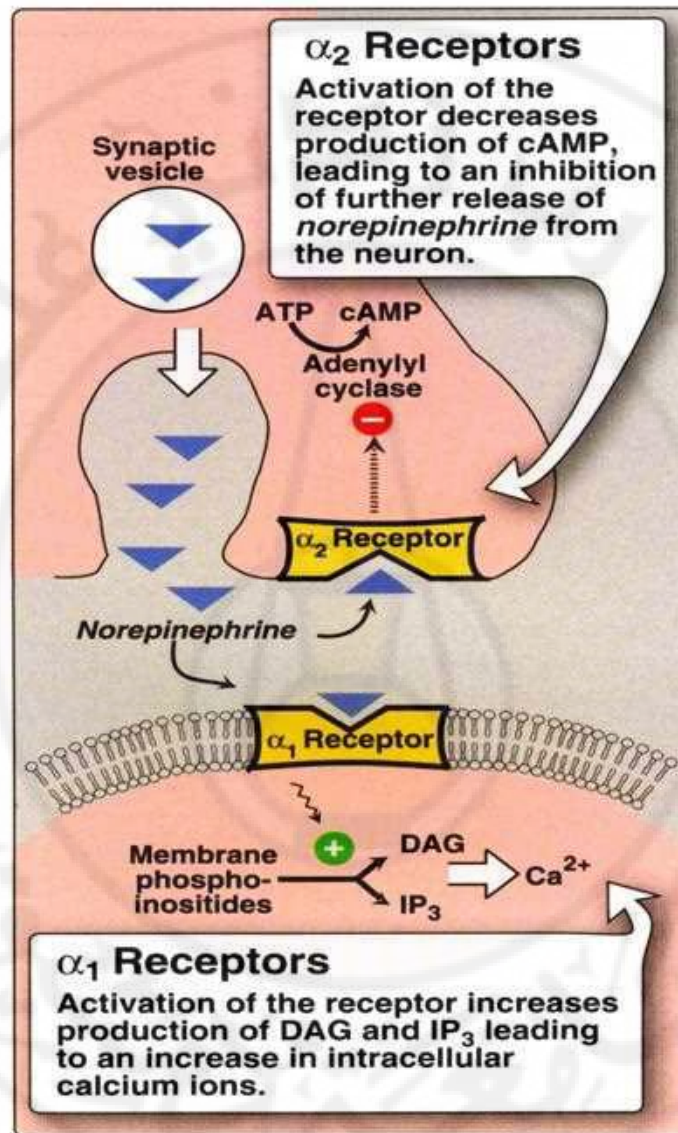


Figure 6.5

Second messengers mediate the effects of α receptors. DAG = diacylglycerol; IP_3 = inositol trisphosphate.



Mechanism of action

- ❖ Believed to work in the relay area of the solitary nucleus.
- ❖ Act as α_2 - receptors agonists to reduce sympathetic tone to peripheral structures (decrease peripheral resistance, HR, and plasma renin activity).

Clinical Uses



1. Methyldopa (Aldomet)

- *Hypertension.*
- *CHF.*

2. Clonidine (catapres)

Hypertension.

As effective as methyldopa but requires smaller doses.

• *CHF*

3. Guanabenz (Wytensin)

- *Hypertension.*
- *Often combined with thiazide diuretics.*

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Side effects

1.Methyldopa (Aldomet)

- ❖ Plasma volume is increased (body attempt to reestablish homeostasis) leading to mild edema.
- ❖ Sedation, dizziness, and headache (diminish as tolerance develops)
- ❖ Mild bradycardia.
- ❖ Flu- like symptoms with fever.
- ❖ Lupus- like syndrome.
- ❖ Positive Coombs' test with no increase in hemolytic anemia.

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Side effects

2. Clonidine (catapres)

- ❖ High dose will cause interaction with α_1 – receptors leading to vasoconstriction and increase BP.
- ❖ Drowsiness, dizziness, and headache (subside with tolerance).
- ❖ Plasma volume is increased (body's attempt to reestablish homeostasis) leading to mild edema.
- ❖ Mild bradycardia.
- ❖ Xerostomia.
- ❖ Constipation.
- ❖ Patch can cause itching, irritation, and redness.

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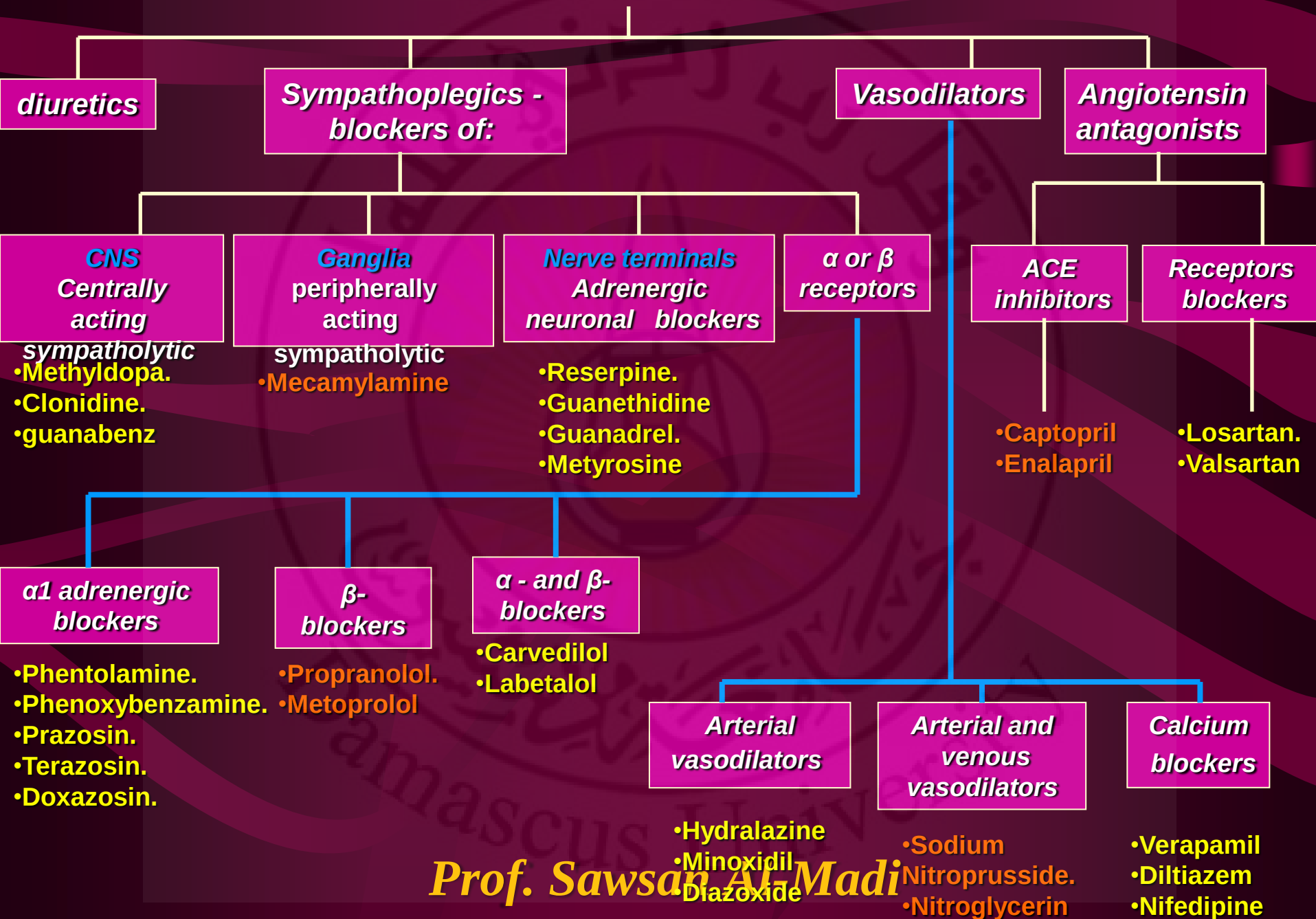
Side effects

3. Guanabenz (Wytensin)

- ❖ Confusion / mental depression.
- ❖ Antimuscarinic side effects.
- ❖ Headache.
- ❖ Nausea.

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Antihypertensive drugs by class



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Pharmacokinetics

Mecamylamine (Inversine)

- **A:** PO.
- **E:** Unchanged in urine

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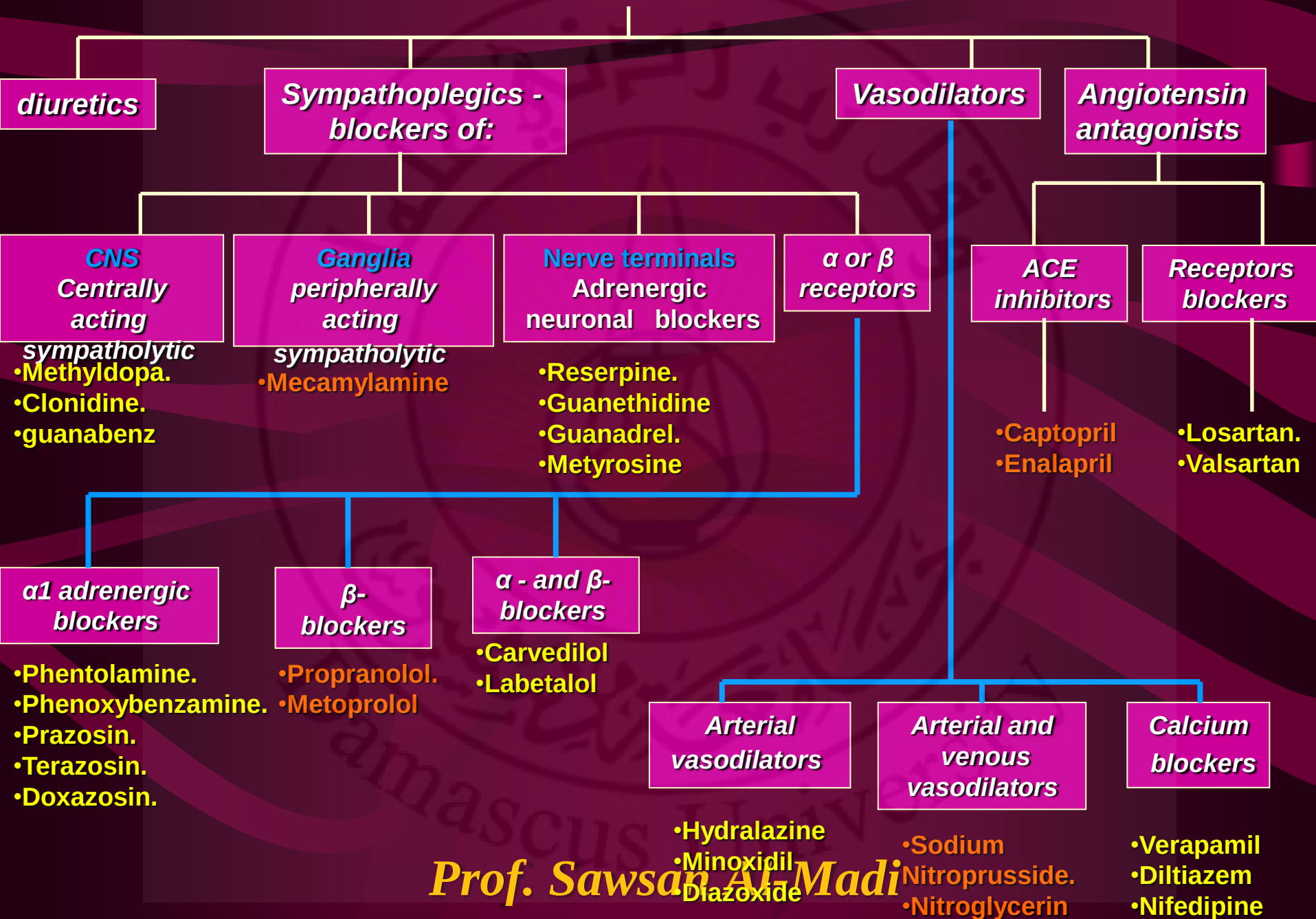
Clinical Uses

❖ **Hypertension.**

(numerous side effects preclude its common use)

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Antihypertensive drugs by class



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Pharmacokinetics

Reserpine

-  **A:** PO.
-  **M:** Hepatic metabolism.
-  **E:** Parent drug and metabolites excreted in urine and feces.

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Pharmacokinetics

Guanethidine & Guanadrel

-  **A:** PO.
-  **M:** Hepatic metabolism.
-  **E:** Parent drug and metabolites excreted in urine.

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Clinical Uses

Reserpine

- Mild hypertension.
- Used only rarely (due to CNS side effects) in small doses with other drugs like diuretics and β - blockers.

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Clinical Uses

Guanethidine & Guanadrel

- Moderate to severe hypertension.

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Side effects

Reserpine

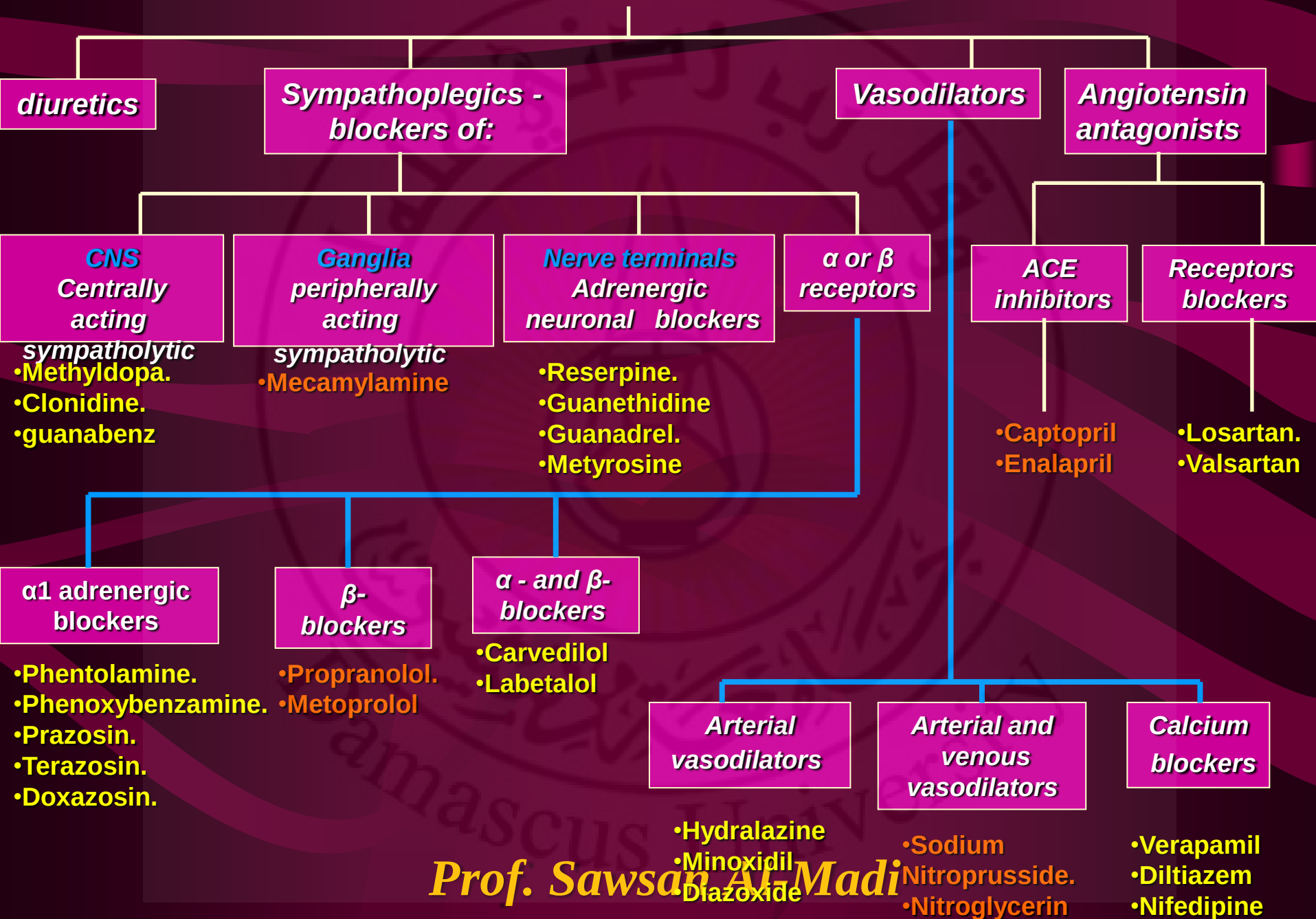
-  Severe depression.
-  Suicide.
-  Sedation.
-  Bradycardia.

Side effects

Guanethidine & Guanadrel

- 🚚 Angina.
- 🚚 Edema (peripheral and pulmonary).
- 🚚 Fatigue.
- 🚚 Severe diarrhea

Antihypertensive drugs by class



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α -adrenergic blockers

1) Nonselective α -adrenergic blockers.

2) Selective α -adrenergic blockers

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α - adrenergic blockers

1) Nonselective α - adrenergic blockers.

A. *Phentolamine.*

B. *Phenoxybenzamine.*

2) Selective α - adrenergic blockers

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- ***α – Adrenergic blockade leads to decreased systemic vascular resistance.***
- ***Results in decreased BP***

α -adrenergic blockers

- 1) Nonselective α -adrenergic blockers.
- 2) Selective α -adrenergic blockers.
 - A. Prazosin.
 - B. Terazosin.
 - C. Doxazosin.

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Pharmacokinetics

Prazosin

- **A:** PO.
- **M:** Hepatic metabolism to active metabolites.
- **E:** Parent drug and metabolites excreted in bile and feces.

Terazosin

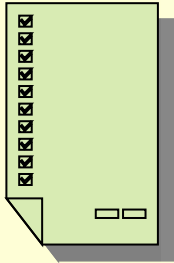
- **A:** PO.
- **M:** Hepatic metabolism to active metabolites.
- **E:** Parent drug and metabolites excreted in urine and feces.

Pharmacokinetics

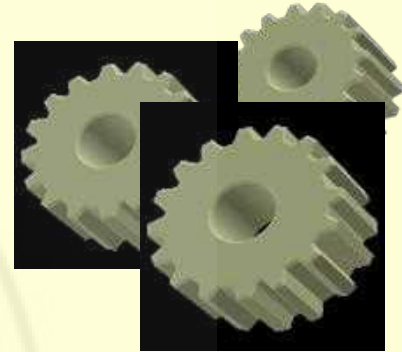
Doxazosin

- **A:** PO.
- **M:** Hepatic metabolism.
- **E:** Parent drug and metabolites excreted in bile and feces.

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Mechanism of action



Prazosin, Terazosin & Doxazosin

- ***α – Adrenergic blockade leads to decreased systemic vascular resistance.***
- ***Results in decreased BP***

Clinical Uses

☞ **Prazosin, Terazosin & Doxazosin**

- Hypertension.
- Causes less reflex tachycardia than nonselective α -adrenergic blockers

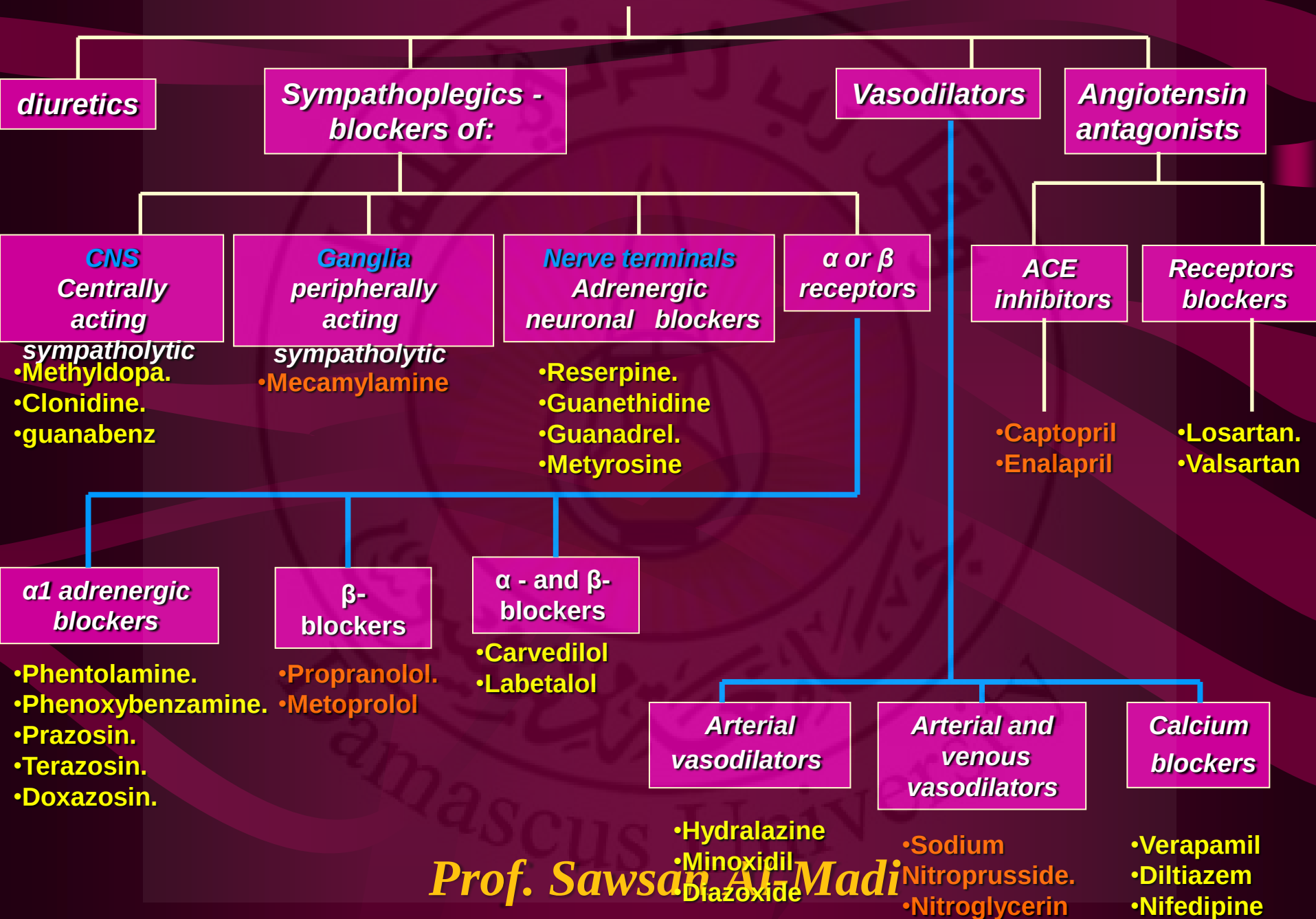
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Side effects

- ☐ **First dose orthostatic hypotension (can lead to syncope) requires careful dosing (usually before bed).**
- ☐ **Dizziness.**
- ☐ **Drowsiness.**
- ☐ **Headache.**
- ☐ **Peripheral edema.**
- ☐ **Palpitations.**

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Antihypertensive drugs by class



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Pharmacokinetics

Propranolol & Metoprolol

-  **A:** PO and IV; well absorbed.
-  **M:** Hepatic metabolism.
-  **E:** Metabolites excreted in urine.

Pharmacokinetics

Labetalol

-  **A:** PO and IV.
-  **M:** Hepatic metabolism.
-  **E:** Parent drug and metabolites excreted in urine and feces.

Carvedilol

-  **A:** PO.
-  **M:** Extensive first - phase hepatic metabolism; metabolized by P450 enzymes.
-  **E:** Parent drug and metabolites excreted in urine and feces.



Mechanism of action

Metoprolol

- ❖ Selective β_1 - blocker.
- ❖ The same as in Propranolol

Propranolol

- Nonselective β - blocker.
- Blocks β_1 - receptors in the heart, increasing sympathetic activity and decreasing BP.
- β_1 - Blockade of the juxtaglomerular apparatus leads to decreased renin release (less angiotensin formation).

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Mechanism of action

Carvedilol

- ❖ β - and α - Blocker.
- ❖ Similar actions as Labetalol

Labetalol

- Nonselective β - blocker (predominant activity) with selective α_1 - blocker activity.
- Decreases HR, decreases plasma renin activity, and increases plasma volume (β - blockade).
- Decreases peripheral vascular resistance (α - blockade).
- α - Blocker activity counteracts vasoconstriction that leads to cold toes and fingers that is associated with β - blockers.

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Clinical Uses



Propranolol

- ❖ Hypertension.
- ❖ Other uses include angina, cardiac arrhythmias, migraine, acute MI, essential tremor.

Clinical Uses



Metoprolol

- ❖ Hypertension.
- ❖ Other uses include angina, CHF acute MI.
- ❖ Less side effects than nonselective β - blocker.

Prof. Dr. Sultan M. Alkhalaf

Clinical Uses



Labetalol

❖ **Hypertension.**

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Clinical Uses



Carvedilol

- ❖ Hypertension.
- ❖ CHF

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Side effects

☞ Propranolol & Metoprolol

- ❖ Contraindicated in patients with asthma, COPD, diabetes mellitus, or peripheral vascular disease.
- ❖ Bronchoconstriction.
- ❖ Hypotension.
- ❖ Bradycardia.
- ❖ Sexual dysfunction.

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Figure 19.8
Some adverse effects of β -blockers.

Side effects

Labetalol

- ❖ Postural hypotension.
- ❖ Dizziness.
- ❖ Nausea.
- ❖ Fatigue.

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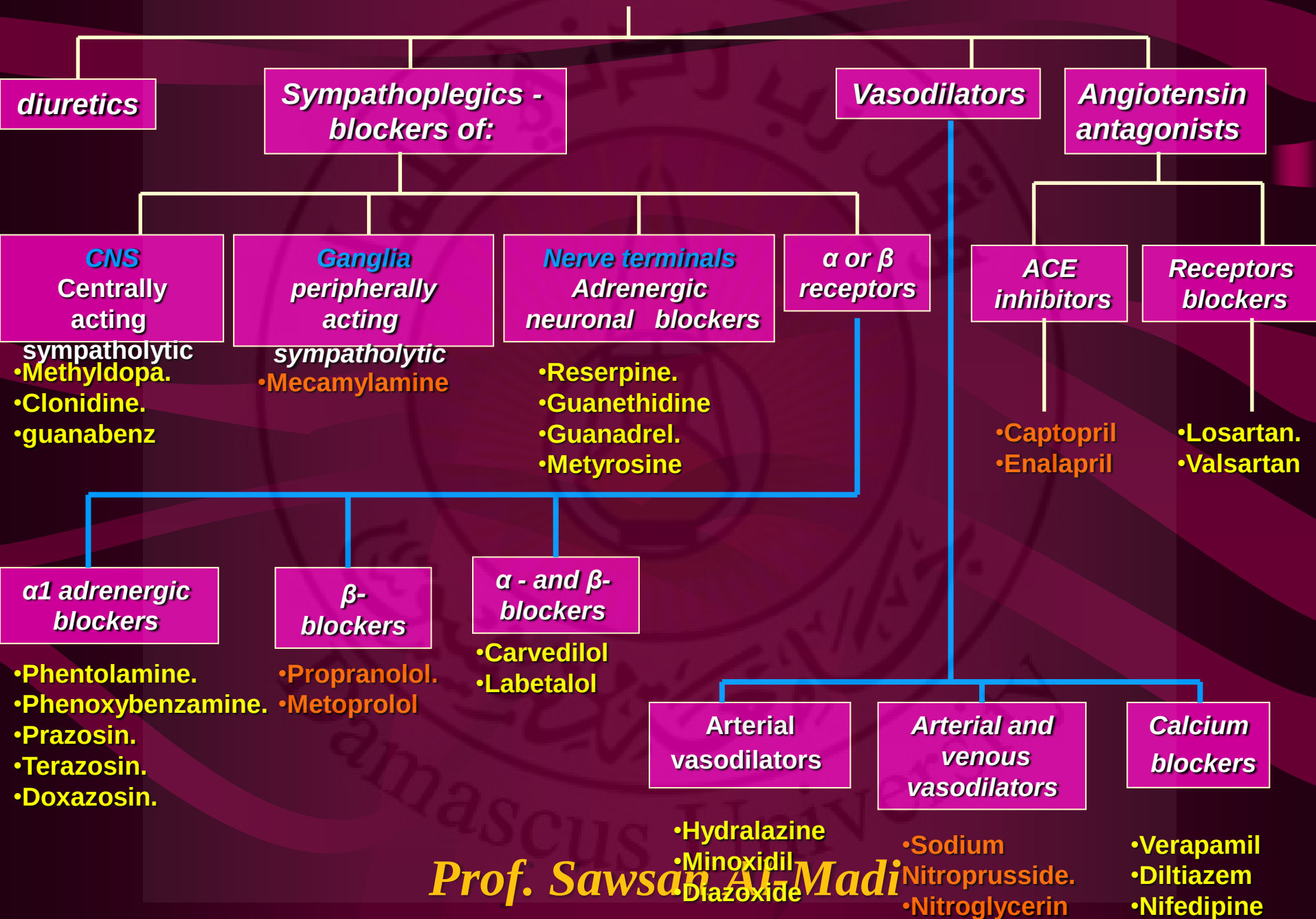
Side effects

Carvedilol

- ❖ **Bradycardia.**
- ❖ **Dizziness.**
- ❖ **Hypotension.**

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Antihypertensive drugs by class



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Pharmacokinetics

Hydralazine

 **A:** PO, IM, and IV.

 **M:** Extensive first - pass hepatic metabolism; hepatic acetylation (remember that certain patient populations have varying rates of acetylation)

 **E:** Metabolites excreted in urine.

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Pharmacokinetics

Minoxidil

-  **A:** PO, and topical.
-  **M:** Hepatic metabolism.
-  **E:** Metabolites excreted in urine.

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Pharmacokinetics

Diazoxide

-  **A:** PO or IV.
-  **M:** Partial hepatic metabolism.
-  **E:** Parent drug and metabolites excreted in urine.

Mechanism of action

Hydralazine

Arterial smooth muscle relaxation and vasodilation (probably through action on cAMP and Ca^{+2}).

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Mechanism of action

Diazoxide

- ◆ **Decreases peripheral vascular resistance via direct vasodilatory effect on smooth muscle in peripheral arterioles.**

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Clinical Uses

Minoxidil

- ❖ Hypertension.
- ❖ Alopecia.

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Clinical Uses

Diazoxide

- ❖ **Acute hypertensive emergencies.**
- ❖ **Hypoglycemia (secondary to hyperinsulinemia via inhibition of insulin release) .**

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Side effects

- Toxicity in slow acetylators.
- Tachycardia.
- Headache.
- Dizziness.
- Nausea.
- Sweating.
- Flushing.
- Nasal congestion.
- Lupus –like syndrome



Hydralazine

Side effects

- Tachycardia.
- Massive fluid retention.
- Hypertrichosis (hair growth).
- ECG changes.
- Pericarditis.

Minoxidil



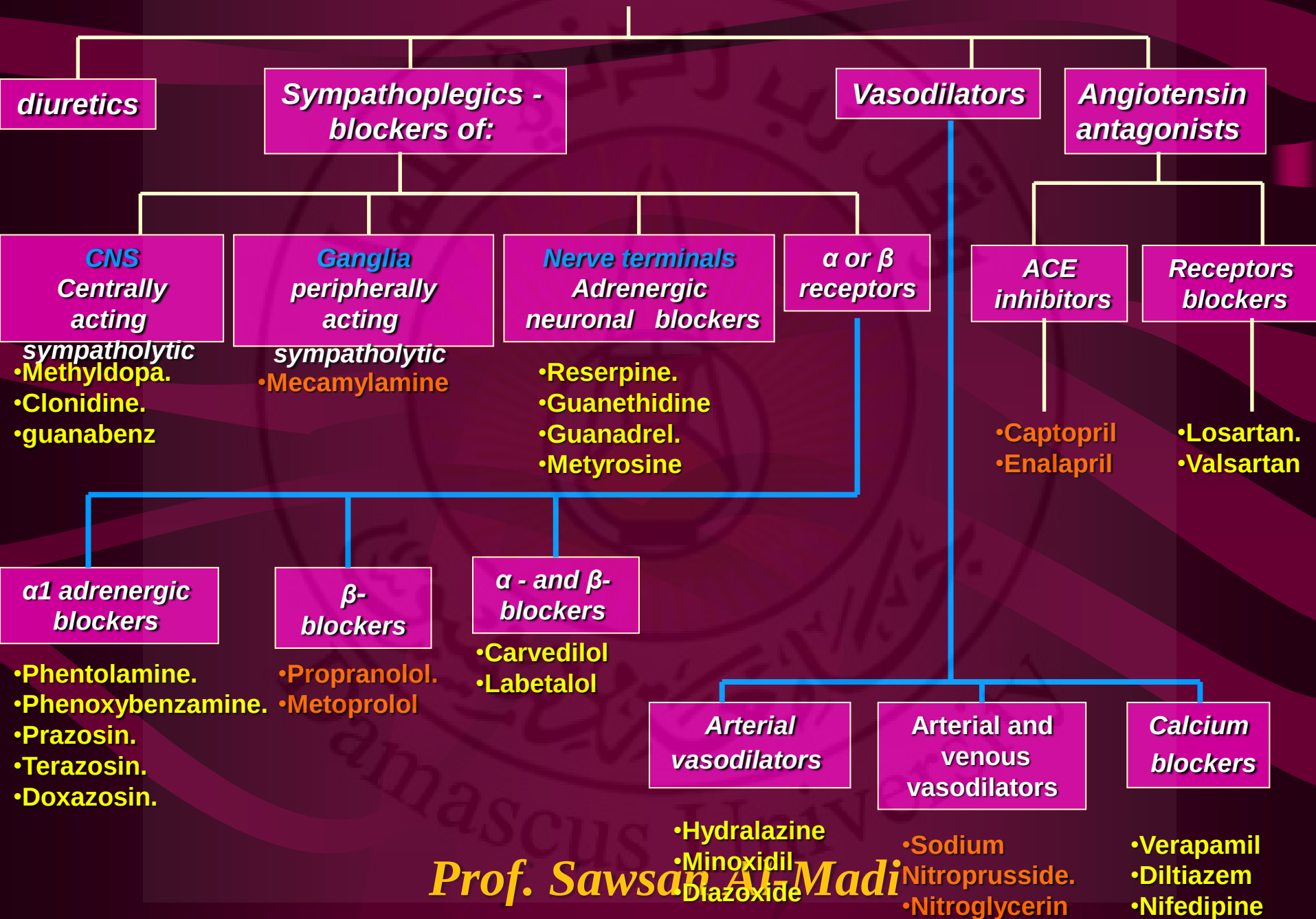
Side effects

Diazoxide

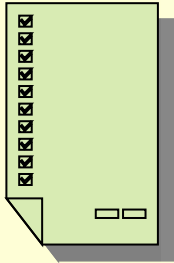


- Reflex tachycardia.

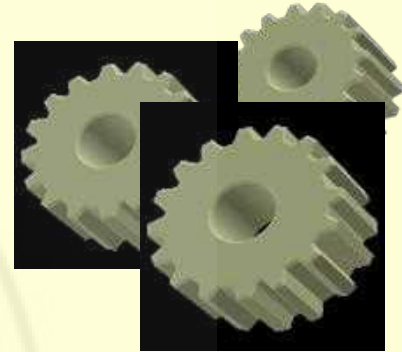
Antihypertensive drugs by class



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Mechanism of action



Sodium Nitroprusside

- ***Dilates arteries and veins***

Clinical Uses

Sodium Nitroprusside

- ☒ Acute hypertensive emergencies.
- ☒ CHF.

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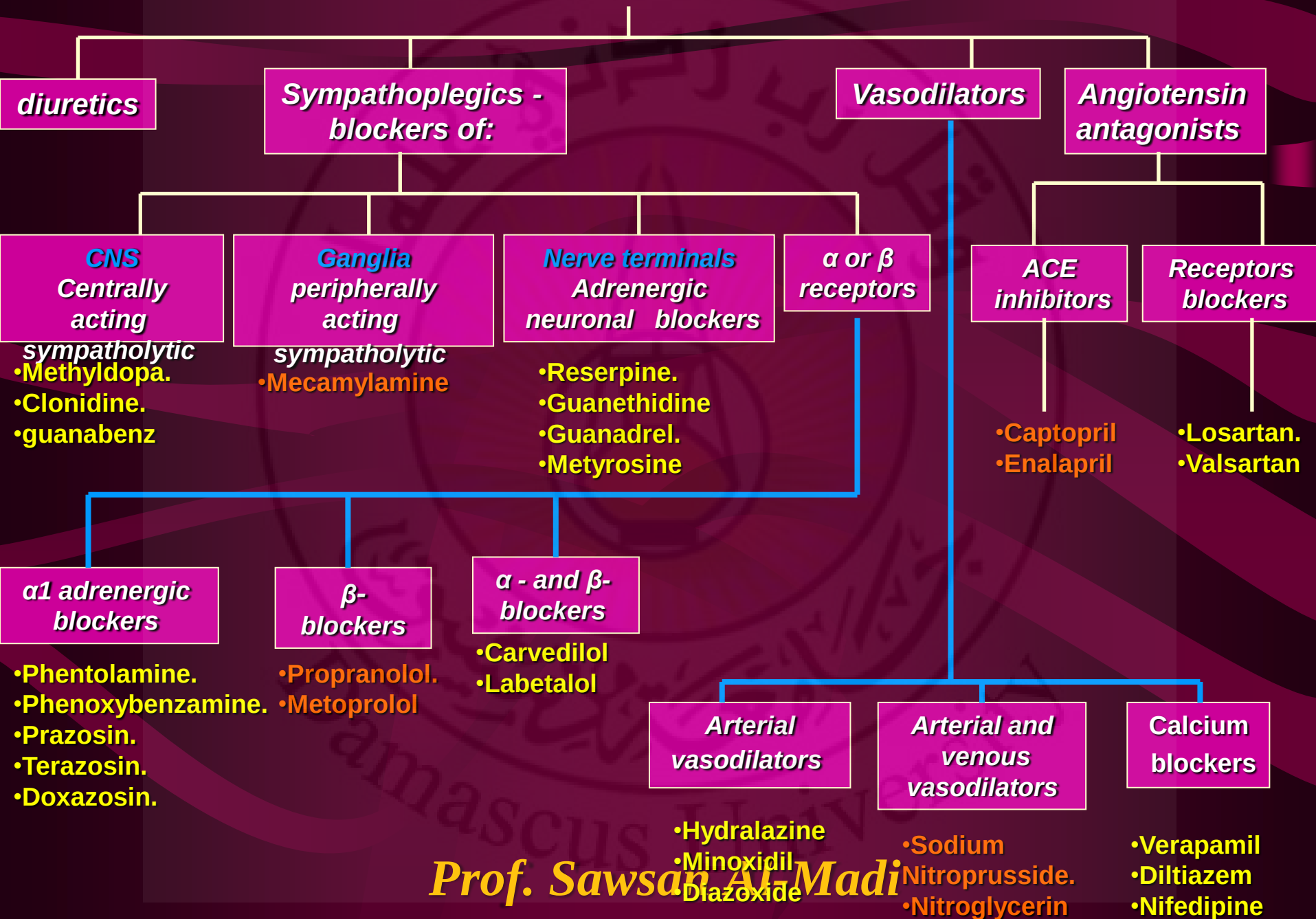
Side effects

Sodium Nitroprusside

-  Byproduct of metabolism is cyanide, which is metabolized by the liver by rhodanase to thiocyanate (water soluble and excreted in urine).
-  Cyanide poisoning in patients with poor diets (alcoholics) where it leads to decreased sulfur availability or when administered in high doses for long period of time.
-  Drug is broken down by UV light so IV bag must be wrapped in foil.

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Antihypertensive drugs by class



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Pharmacokinetics

Diltiazem

-  **A:** PO and IV.
-  **M:** Extensive first - pass hepatic metabolism; metabolized by P450 enzymes to less active metabolites.
-  **E:** In urine and feces.

Verapamil

-  **A:** PO and IV.
-  **M:** Extensive first - pass hepatic metabolism; metabolized by P450 enzymes to active metabolite.
-  **E:** In urine and feces.

Pharmacokinetics

Nifedipine

 **A:** PO.

 **M:** Extensive first - pass hepatic metabolism; metabolized by P450 enzymes to inactive metabolites.

 **E:** in urine and feces.

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Side effects

- ▶ **Peripheral edema.**
- ❖ **Hypotension.**
- ▶ **Palpitations due to reflex tachycardia.**
- ▶ **Dizziness and headache.**
- ❖ **Constipation.**
- ❖ **Nausea.**
- ▶ **Abdominal cramps.**

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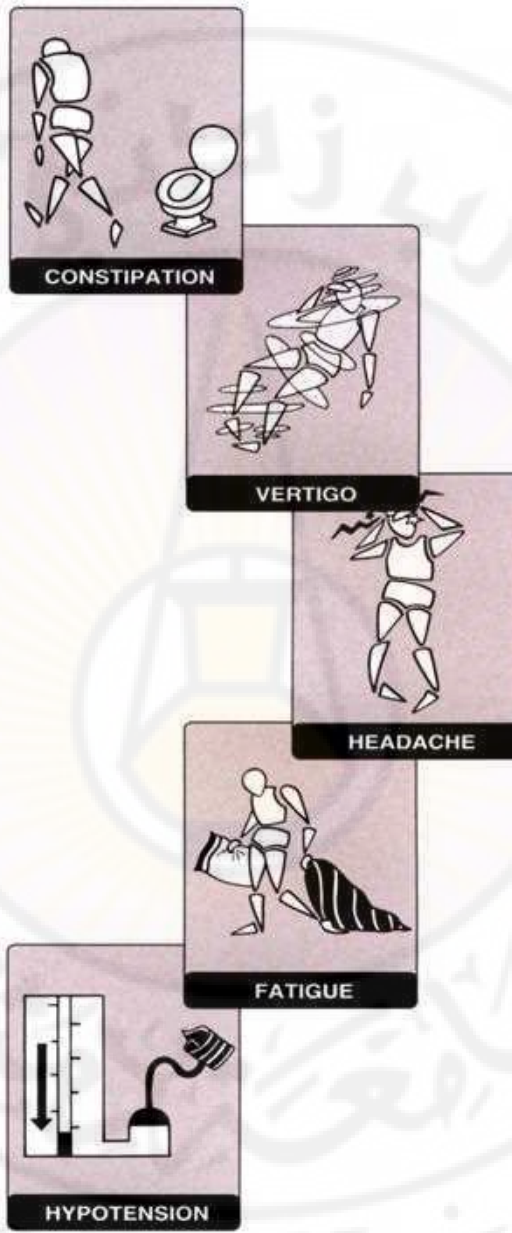
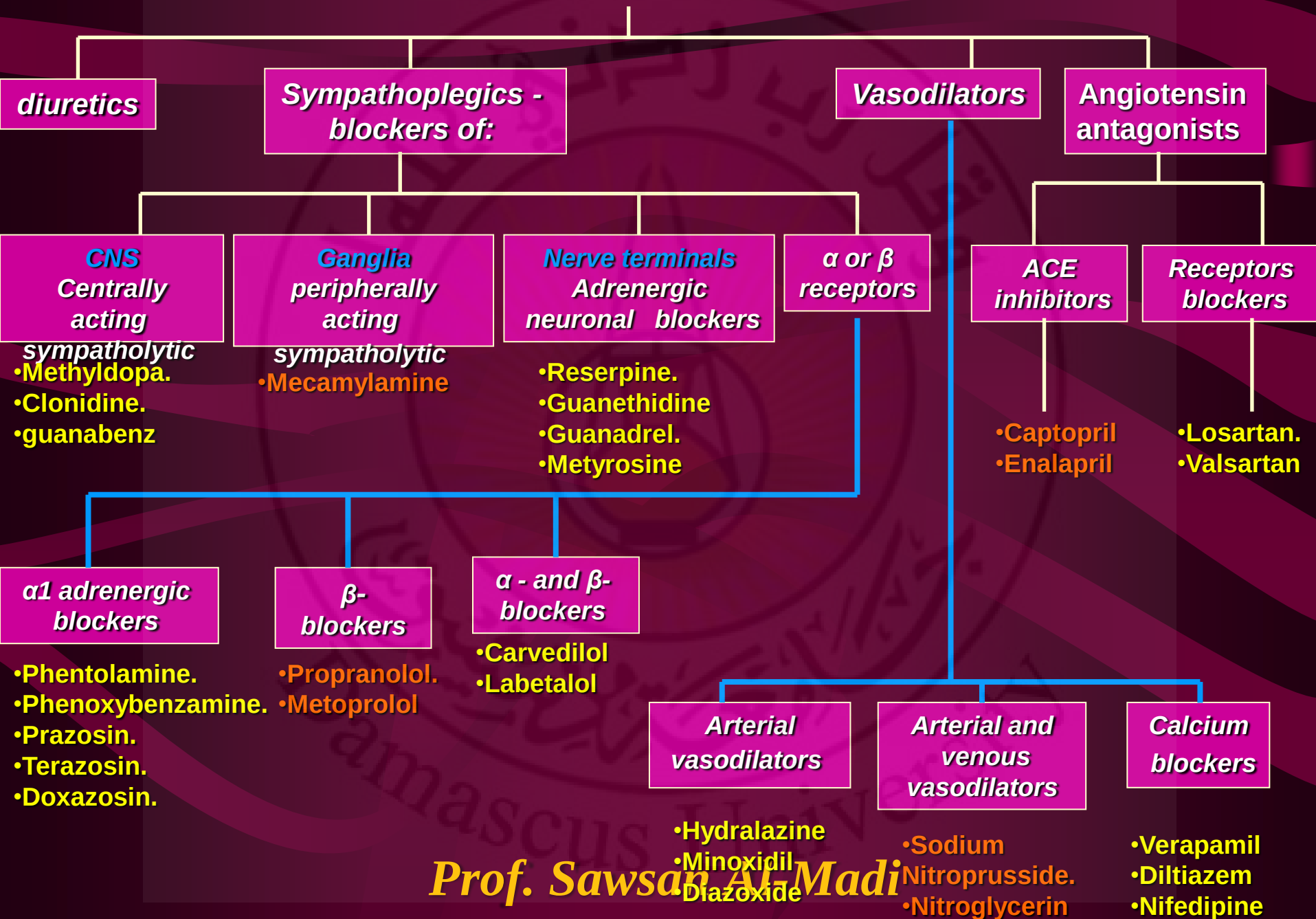
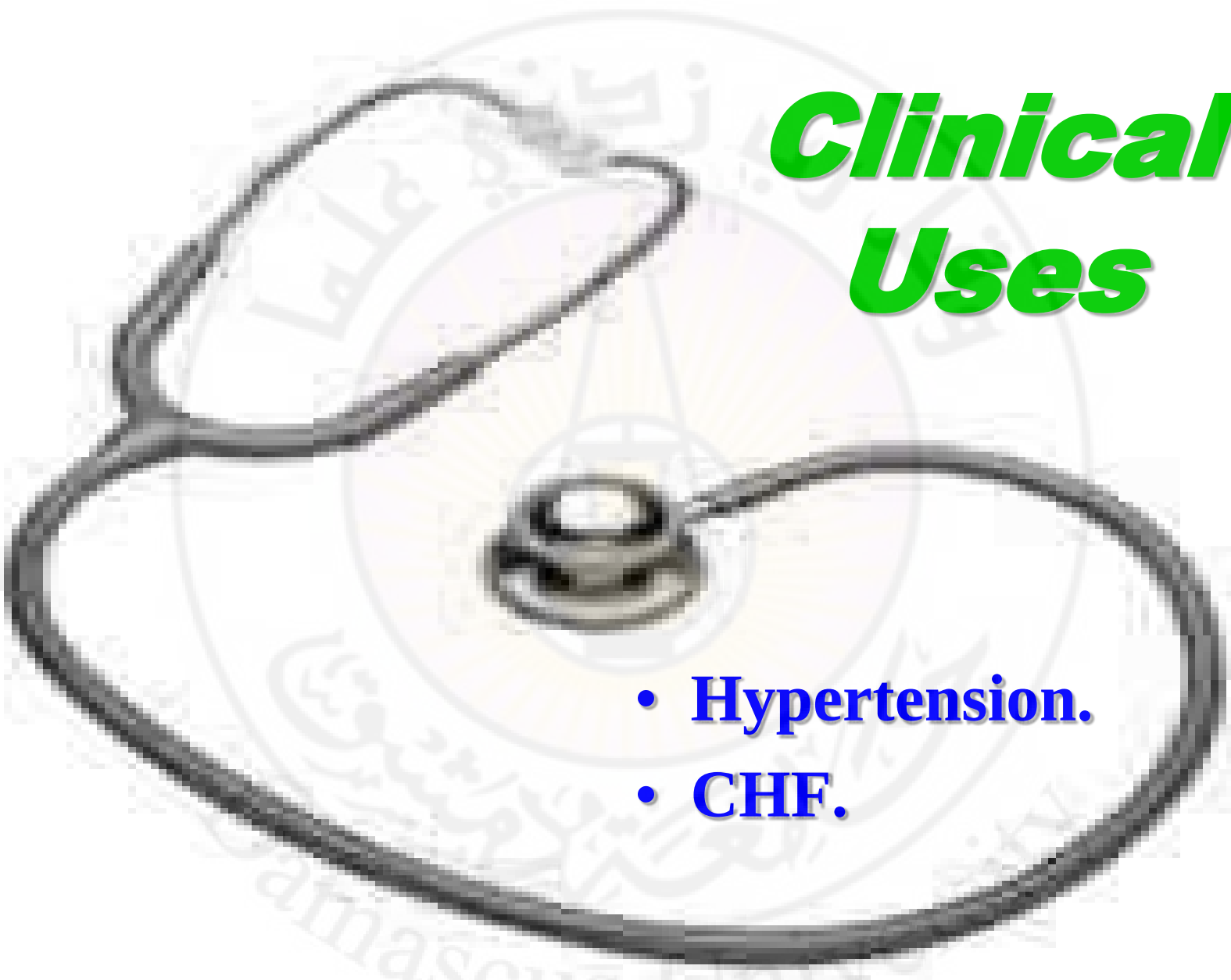


Figure 19.13
Some common adverse effects of the calcium channel blockers.

Antihypertensive drugs by class



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Clinical Uses

- **Hypertension.**
- **CHF.**

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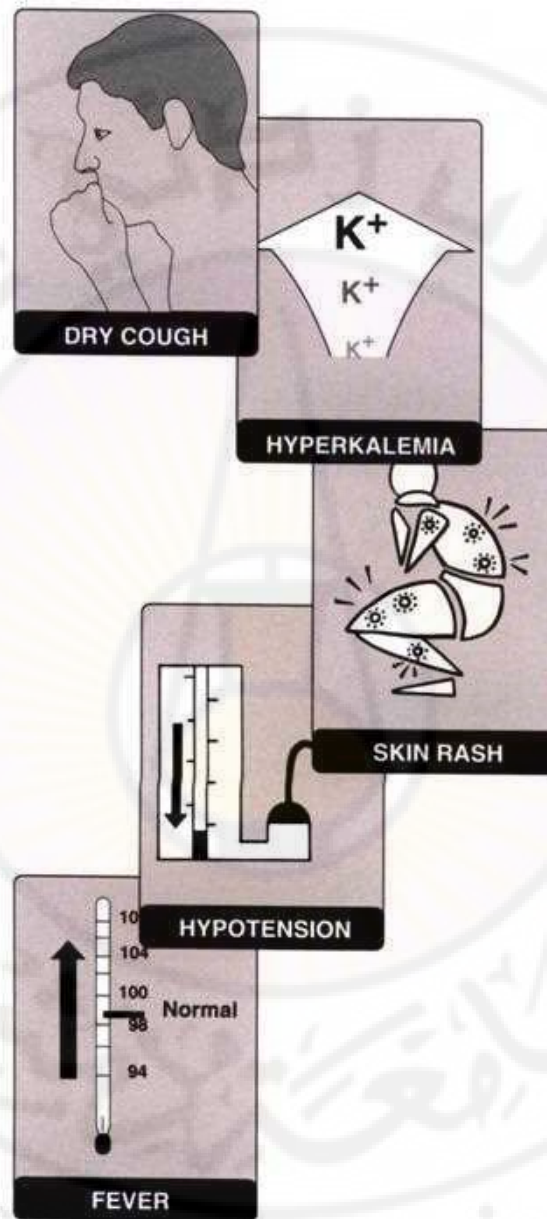


Figure 19.10

Some common adverse effects of the ACE inhibitors.

Side effects

❖ *Bradykinin increase leading to cough and skin rash.*

❖ *Teratogenesis.*

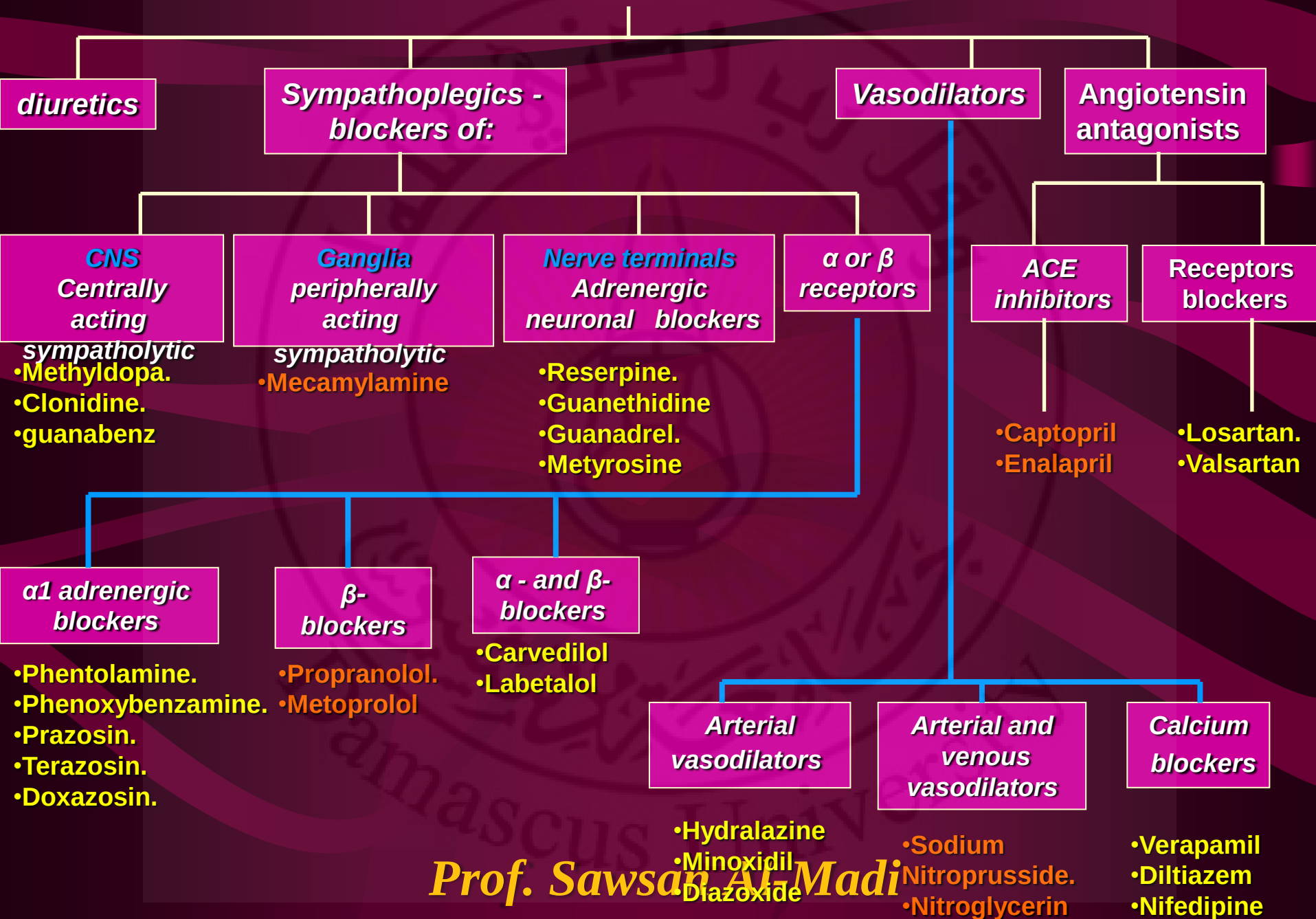
❖ *Hyperkalemia.*

❖ *Neutropenia.*

❖ *Hypotension.*

❖ *Acute renal failure.*

Antihypertensive drugs by class



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Pharmacokinetics

Losartan & Valsartan

 **A** PO.

 **M** Hepatic metabolism by CYP2C9 and CYP3A4 system.

 **E** Parent drug and metabolite excreted in urine and feces.

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Mechanism of action

Losartan & Valsartan

- **Angiotensin I receptor blockade prevents the vasoconstriction caused by Angiotensin I.**

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Clinical Uses



**Losartan
&
Valsartan**

❖ **Hypertension.**

❖ **CHF**

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Side effects

Losartan & Valsartan

- ❖ **Smaller incidence of side effects than ACE inhibitor.**
- ❖ **No bradykinin increase (no cough or rash)**

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Risk Factors

- ***Age - Risk becomes higher in the elderly***
- ***A family history of hypertension***
- ***Gender - Risk is higher in men than in women***
- ***Smoking***
- ***Diabetes***
- ***Obesity***
- ***Stress***

شكراً على الإصغاء

Damascus University

Cardiovascular system





Coronary Heart Disease (CHD)

Antianginal Drugs



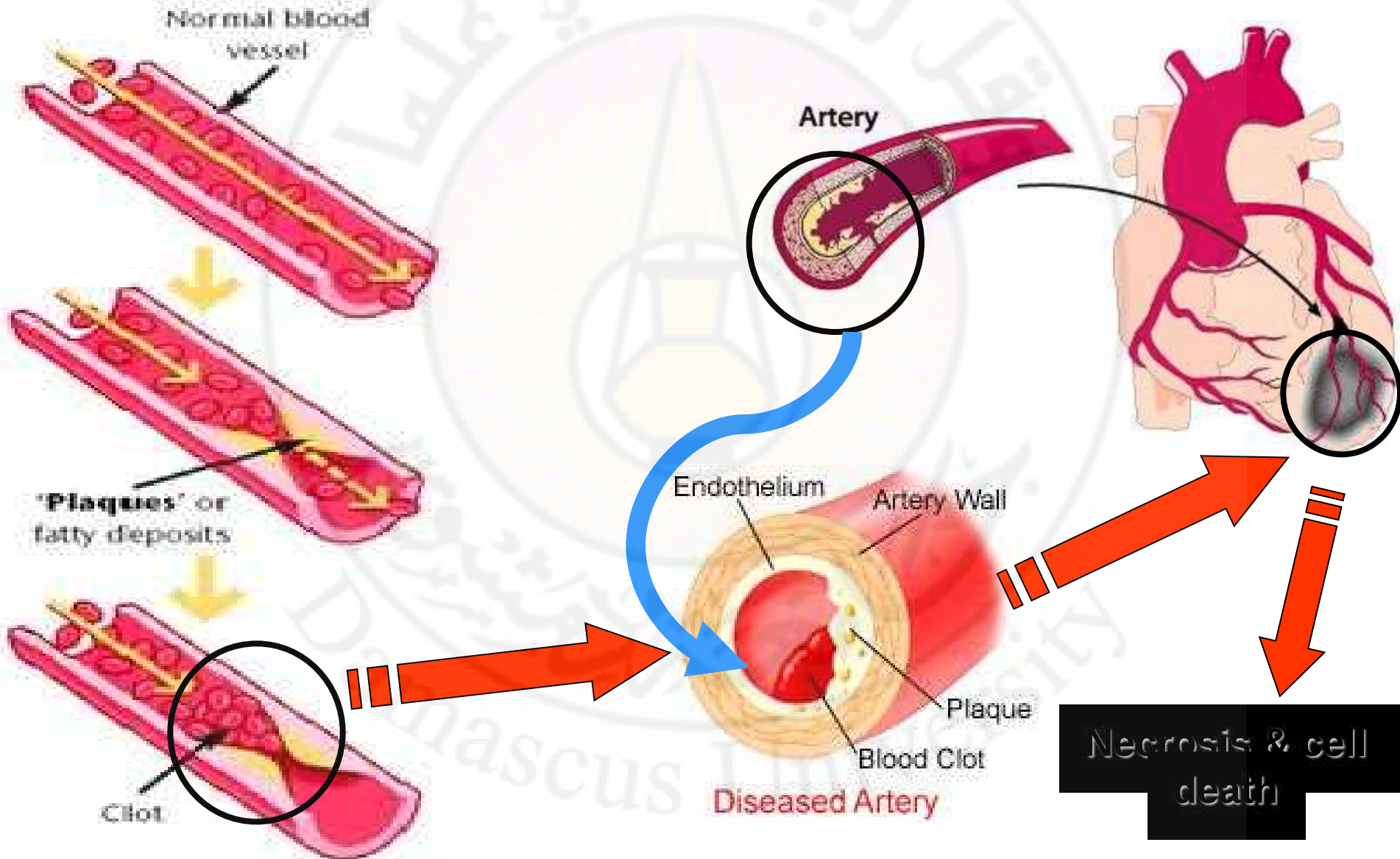
Antihyperlipidemic Drugs

Drugs affecting Coagulation

MI is one of the leading causes of death. Death usually results from cardiac damage or complications. Mortality is about 25%. However, more than 50% of sudden deaths occur within 1 hour after the onset of symptoms, before the patient reaches the hospital. Of those who recover, up to 10% die within a year.

Men are more susceptible to MI than premenopausal women, although the incidence is increasing in women who smoke and take oral contraceptives. The incidence in postmenopausal women is similar to that in men.

Pathophysiology of Myocardial Infarction



What to do during an *Angina* attack

At the first sign of chest pain:

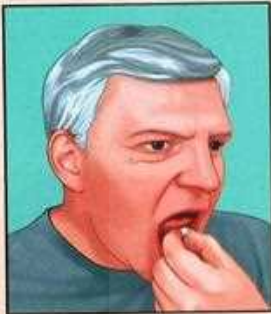


1. Sit down and rest immediately. Wait for a few minutes.

2. If symptoms are not gone in 2-3 minutes, place your **FIRST** *nitroglycerin* tablet under your tongue (or between your gum and inside cheek), or use your spray.

- Do not chew or swallow the tablet.
- Do not drink, eat, or smoke while the nitroglycerin is in your mouth.

You may experience a slight stinging or burning sensation. This is normal and means the *nitroglycerin* is working.

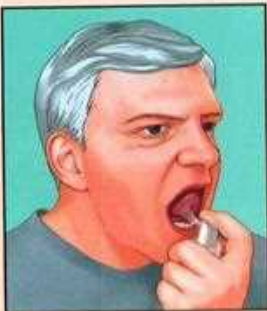


Place the tablet under your tongue and allow it to dissolve.

3. If the symptoms still persist after a further 3-5 minutes, use a **SECOND** tablet (or spray).

4. Wait 3-5 minutes and if symptoms still persist, use a **THIRD** tablet (or spray).

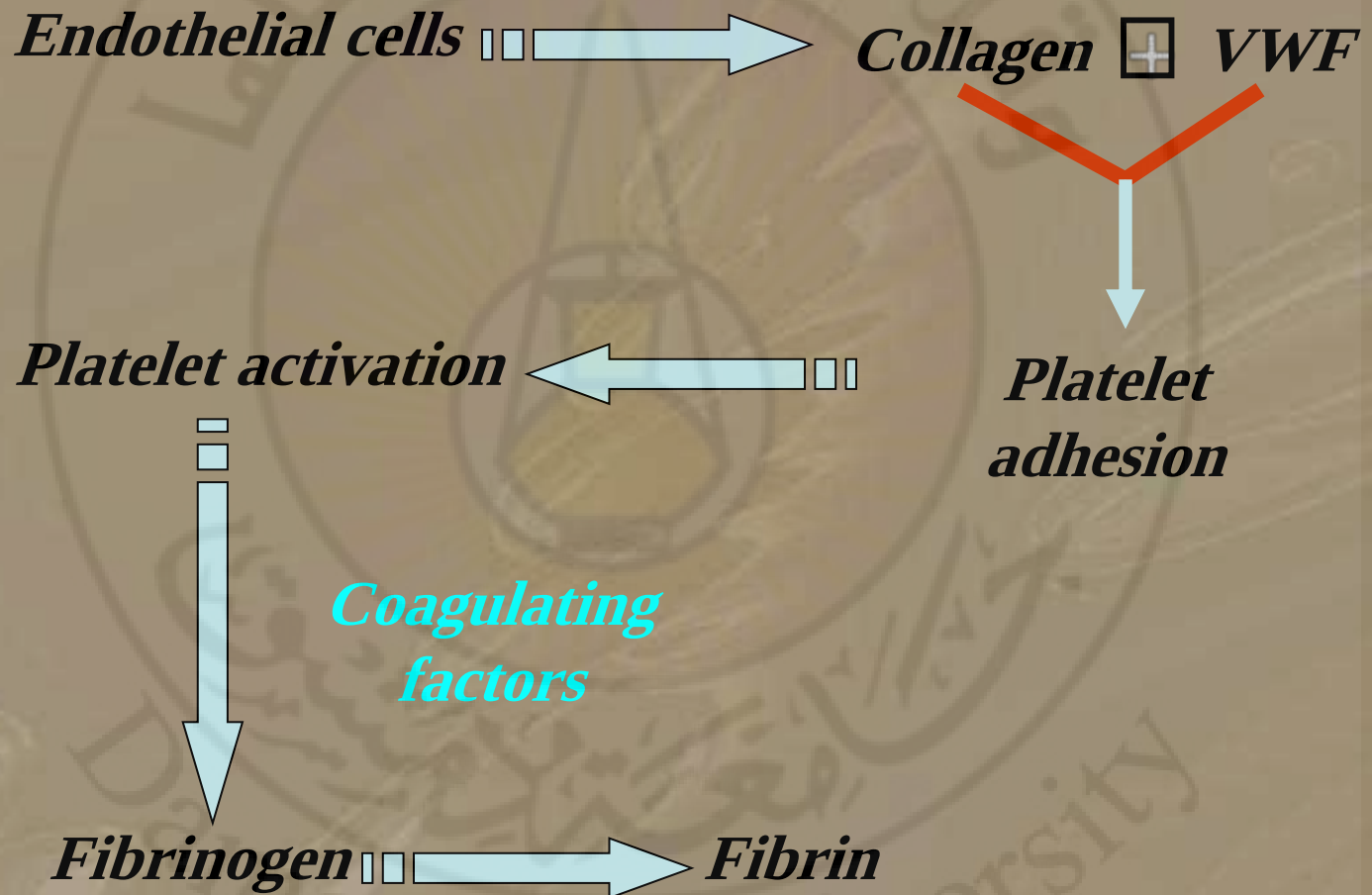
5. If your *Angina* is still present after the **THIRD** tablet (or spray), and at least 15 minutes after you first started to feel discomfort, call your healthcare provider, or ask someone to take you to the nearest hospital emergency room.



Spray directly under your tongue.
DO NOT INHALE

Treating MI

- Treatment for MI has three goals:
 - to relieve chest pain
 - to stabilize heart rhythm
 - to reduce cardiac work load.



*Coagulating
factors*

Fibrinogen → *Fibrin*

Myocardial Infarction



Reperfuse ischemic tissue

Streptokinase converts plasminogen to plasmin. Plasmin digests fibrin and fibrinogen, thus dissolving clots.

Antianginal agents (above).

Management of Myocardial Infarction



Analgesia

Intravenous opiates (initially morphine sulphate 10 mg or diamorphine 5 mg) and antiemetics (initially cyclizine 50 mg or prochlorperazine 12.5 mg) should be administered through an intravenous cannula and titrated against the response by giving repeated small aliquots until the patient is comfortable.

Intramuscular injections should be avoided because the clinical effect may be delayed by poor skeletal muscle perfusion and a painful haematoma may form following thrombolytic therapy.

Thrombolytic drugs

Coronary thrombolysis helps restore coronary patency (see Fig. 3.69), preserves left ventricular function, and improves survival. Successful thrombolysis leads to reperfusion with relief of pain, resolution of acute ECG changes and sometimes transient arrhythmias. The sooner the patient is treated, the better the results will be; any delay will only increase the extent of myocardial damage—‘minutes mean muscle’.

Streptokinase, 1.5 million units in 100 ml of saline given as an intravenous infusion over 1 hour, is a widely used regimen. Streptokinase is relatively cheap (approximately £60–£80 per dose in the UK) but is antigenic and occasionally causes serious allergic manifestations. The drug may also cause hypotension, which can often be managed by stopping and restarting the infusion at a slower rate. Circulating neutralising antibodies are formed following treatment with streptokinase and may persist for 5 years or more. These antibodies can render subsequent infusions of streptokinase ineffective so it is advisable to use another agent if the patient requires further thrombolysis in the next few years.

Alteplase (human tissue plasminogen activator or tPA) is a genetically engineered drug and is approximately 10 times more expensive than streptokinase; it is not antigenic and seldom causes hypotension. The standard regimen is given over 90 minutes (bolus dose of 15 mg, followed by 0.75 mg/kg of body weight, but not exceeding 50 mg, over 30 minutes and then 0.5 mg/kg body weight, but not exceeding 35 mg, over 60 minutes). As it is so expensive many units only use tPA if streptokinase is contraindicated by virtue of allergy, previous exposure, or profound hypotension. However, there is evidence that the drug may produce slightly better survival rates than streptokinase, particularly among high-risk patients.

Table 34-3. Properties of thrombolytic enzymes.

Agent	Source	Duration of Action	Comments
Alteplase, reteplase	Recombinant human protein	2-10 min	Active tissue plasminogen activator, (t-PA); converts plasminogen to plasmin; intravenous infusion (alteplase) or bolus doses (reteplase) required. Most expensive. Reteplase is somewhat longer-acting than alteplase
Anistreplase	Prodrug: streptokinase plus recombinant human plasminogen	1-2 hours	Slowly releases streptokinase-activated plasminogen; single bolus administration provides long duration of action
Streptokinase	Bacterial product	20-25 min	Streptokinase combines with plasminogen; the combination activates plasminogen to plasmin; intravenous infusion required. Least expensive
Urokinase	Human kidney cell culture	< 20 min	Active plasminogen activator

RELATIVE CONTRAINDICATIONS TO THROMBOLYTIC THERAPY (POTENTIAL CANDIDATES FOR PRIMARY ANGIOPLASTY)

- Active internal bleeding
- Previous subarachnoid or intracerebral haemorrhage
- Uncontrolled hypertension
- Recent surgery (within 1 month)
- Recent trauma (including traumatic resuscitation)
- High probability of active peptic ulcer
- Pregnancy

Anticoagulants

Subcutaneous heparin (12 500 units twice daily for 7 days or until discharge from hospital), given in addition to oral aspirin, may prevent reinfarction after successful thrombolysis and reduce the risk of thromboembolic complications. Clinical trials have shown that this form of therapy produces a small reduction in short-term mortality (approximately 5 lives saved per 1000 patients treated) but also increases the risk of cerebral haemorrhage (0.56% versus 0.4%) and of other bleeding complications (1% versus 0.8%).

Aspirin

Oral administration of 75–300 mg aspirin daily improves survival (30% reduction in short-term mortality) on its own, and enhances the effect of thrombolytic therapy. The first tablet (300 mg) should be given in a soluble or chewable form and the therapy should be continued indefinitely if there are no unwanted effects.

Nitrates and other agents

Sublingual glyceryl trinitrate (300–500 μg) is a valuable first-aid measure in threatened infarction, and intravenous nitrates (nitroglycerin 0.6–1.2 mg/hour or isosorbide dinitrate 1–2 mg/hour) are useful for the treatment of left ventricular failure and the relief of recurrent or persistent ischaemic pain.

Large-scale trials have shown that there is no evidence of a survival advantage from the routine use of oral nitrate therapy, oral calcium antagonists or intravenous magnesium in patients with acute myocardial infarction.

β -adrenoceptor antagonists

Acute β -adrenoceptor antagonist use with intravenous atenolol (5–10 mg given over 5 minutes) or metoprolol (5–15 mg given over 5 minutes) relieves pain, reduces arrhythmias and improves short-term mortality in patients who present within 12 hours of the onset of symptoms, but should be avoided if there is heart failure, heart block or severe bradycardia. Chronic β -adrenoceptor antagonist therapy improves long-term survival, and should be given to all patients who can tolerate it.

M.I. Predisposing factors include:

- aging
- diabetes mellitus
- elevated serum triglyceride, low-density lipoprotein, and cholesterol levels and decreased serum high-density lipoprotein levels
- excessive intake of saturated fats, carbohydrates, or salt
- hypertension
- obesity
- positive family history of CAD
- sedentary lifestyle
- smoking
- stress or a type A personality
- use of amphetamines or cocaine.

شكراً على الإصغاء

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